UNIVERSITY OF ALBERTA

# FACIAL SELECTIVE DIELS-ALDER REACTIONS OF (1R, 5R)-(+)-3-CARBOMETHOXY-6,6-DIMETHYLBICYCLO-[3.1.1]HEPT-3-EN-2-ONE. APPLICATION TO SESQUITERPENOIDS SYNTHESIS

BY

©

**SEW YEU CHEW**

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

DEPARTMENT OF CHEMISTRY

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*Dedicated to my family*

# ABSTRACT

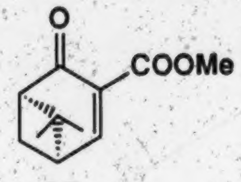
The stereofacially differentiated enone ester **27** was chosen to study the effects of steric influence on the Diels-Alder reaction. In general under Lewis acid catalysis **27** adds to dienes at low to ambient temperatures at a reasonable rate. Yields of predictable chiral adducts are moderate with the unexpected exception of zinc chloride catalyzed reactions which provide good to high yields. In all cases, only products of addition to the *Si*-face of general type **86** were observed. The regiochemistry of the adducts is exclusively that predicted by the *ortho*- and *para*-rules. The stereochemistry shows a high selectivity in favor of ester-*endo* transition state products.

The synthetic potential of dienophile **27** was then illustrated by strategic application to the synthesis of the chiral cadinane sesquiterpenes **34**, **38**, and (+)-artemisinin **44**, an antimalariai component from the Chinese medicinal plant Qinghao.

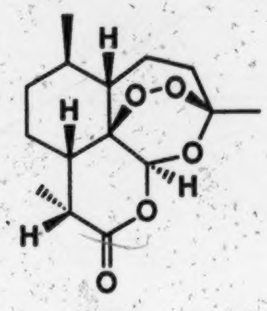
The total syntheses of sesquiterpenes **34** and **38** were achieved in 12 and 13 steps respectively from the Diels-Alder adduct **85**. The key steps included the conversion of **85** into ketone **132**. Fragmentation of the cyclobutane ring of **132** using *p*-toluenesulfonic acid and ethylene glycol provided a mixture of acetals which was transacetalized and epimerized to give ketone **79**. Methyllithium addition to **79** gave two epimeric alcohols **137** and **138**. Alcohol **137** was converted to ester **144** which upon dehydration and reduction gave **38**. Similarly, functional group transformation of alcohol **138** gave ester **149** which was reduced to give **34**. The structure and stereochemistry of the synthetic compound **34** was

determined by X-ray analysis. The stereochemistry of $C_3$ of **38** was rigorously determined by spectroscopic methods including $^1H$ decoupling and NOE experiments. However, their spectral properties were different from those of the natural products.

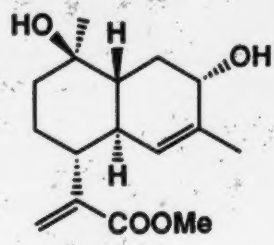
In the synthetic studies of (+)-artemisinin, the key intermediate **164** was prepared in 13 steps from compound **79**. The functional group transformation involved three major operations. First, the introduction of a carbon functionality to $C_2$ stereoselectively. Secondly, the conversion of the isopropenyl group to 1-carbomethoxyethyl and finally the removal of the thioacetal or oxygen equivalent from the cyclohexene ring system.



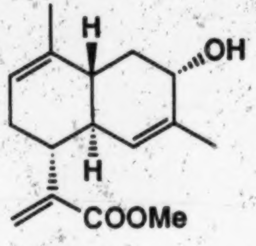
**27**



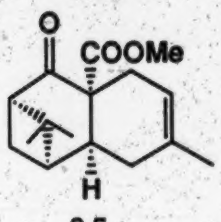
**44**



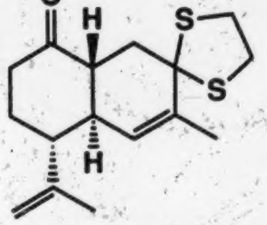
**34**



**38**



**85**



**79**

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| Ac | Acetyl |
| ax | axial |
| APT | Attached Proton Test |
| c. | concentration |
| CIMS | Chemical Ionization Mass Spectrum |
| d | doublet |
| DME | 1,2-Dimethoxymethane |
| DMSO | Dimethyl sulfoxide |
| e | equatorial |
| eq | equivalent |
| Eqn | Equation |
| *gem* | geminal |
| h | hour |
| HRMS | High Resolution Mass Spectrum |
| m | multiplet |
| MCPBA | *meta*-Chloroperoxybenzoic acid |
| Me | Methyl |
| min | minute |
| mp | melting point |
| NMR | Nuclear Magnetic Resonance |
| NOE | Nuclear Overhauser Effect |
| *p* | para |
| psi | pound per square inch |

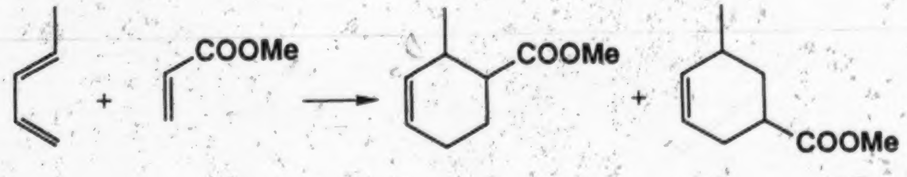
| | |
|---|---|
| q | quartet |
| s | singlet |
| t | triplet |
| THF | Tetrahydrofuran |
| TLC | Thin Layer Chromatography |
| TMS | Tetramethylsilane |

# INTRODUCTION

The reaction between a conjugated diene and an olefin to form a substituted cyclohexene was first observed by Diels and Alder.[1] It is a general class of cycloaddition reaction, and since its formulation in 1928 the Diels-Alder reaction has remained remarkably useful to synthetic organic chemists. It presents an excellent opportunity for the regioselective and stereoselective construction of polycyclic natural products. Over the years, Diels-Alder reactions have been successfully applied to the synthesis of natural products, for example steroids,[2, 3] alkaloids[4, 5] and prostaglandins.[6] Although Diels-Alder reactions have been recognized as one of the most powerful tools in organic synthesis, the detailed mechanism of this reaction, even in the simple case of the reaction between butadiene and ethylene, is still somewhat controversial. While it is now generally agreed that most Diels-Alder reactions are concerted in view of the retention of stereochemistry during reactions, it is still not clear whether all or indeed any are synchronous, the new carbon-carbon bonds being formed to equal extents in the transition state. According to the Woodward-Hoffmann rules[7] the suprafacial approach [$\pi 2s + \pi 4s$] of diene and dienophile is symmetry allowed and consequently can be a synchronous reaction. Also, Houk and co-workers[8] reported that the reaction of butadiene with ethylene is consistent with a synchronous concerted mechanism. On the other hand, calculations according to MINDO/3[9, 10] contradict these results in preferring an unsymmetrical transition state and a biradical-like intermediate.

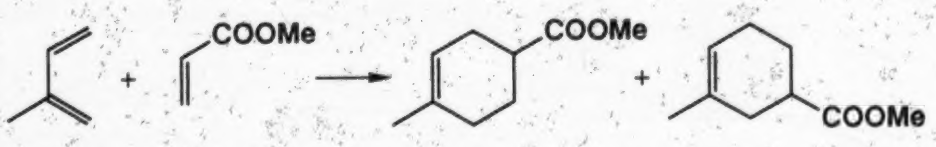
Diels-Alder additions of unsymmetrical dienes and dienophiles show a strong preference for the formation of specific regioisomers.[11-13] The regiochemistry of these additions can be predicted by using a group of orientational rules. In Diels-Alder reactions of electron rich dienes and electron difficient dienophiles, 1-substituted dienes preferentially give the "*ortho*"-isomer, in which the C-1 substituent from the diene component is adjacent (*ortho*) to the substituent from the dienophile. In contrast, 2-substituted dienes mainly give the "*para*"-isomer. For example, the reaction of *trans*-piperylene with methyl acrylate gave adduct **1**[14] as the principle product rather than adduct **2**. Similarly, the reaction of isoprene with methyl acrylate afforded adduct **3**[14] as the major product rather than adduct **4**. The reason for these orientation effects has long been puzzling. Most investigators[15-18] have used a Frontier Molecular Orbital approach in which the regiochemistry is predicted from the primary interaction of the frontier molecular orbitals. Recently, using this approach, Houk[19] predicted that when both the diene and dienophile are electron rich, the "*meta*"-orientation will be favored. The products formed according to the "*meta* rule" has since been observed experimentally by Fleming *et al.*[20] As would be expected, in 1,3-disubstituted butadienes, the directive influence of the substituents is additive. However, the magnitude of the orientational effect differs from one substituent to another and also with position of the substituents on the diene. Therefore, the structure of the adducts obtained will depend on the nature and the disposition of the substituents. The hierarchical order of substituent effects can be exploited to obtain adducts of unusual orientation through the use of proper activating groups in the diene and dienophile. Thus Diels-

Alder product **5**,[21] instead of **6**, was obtained from the reaction of 2-trimethylsilyloxybutadiene and methyl β-nitroacrylate due to the orientational dominance of the nitro group over that of ester.



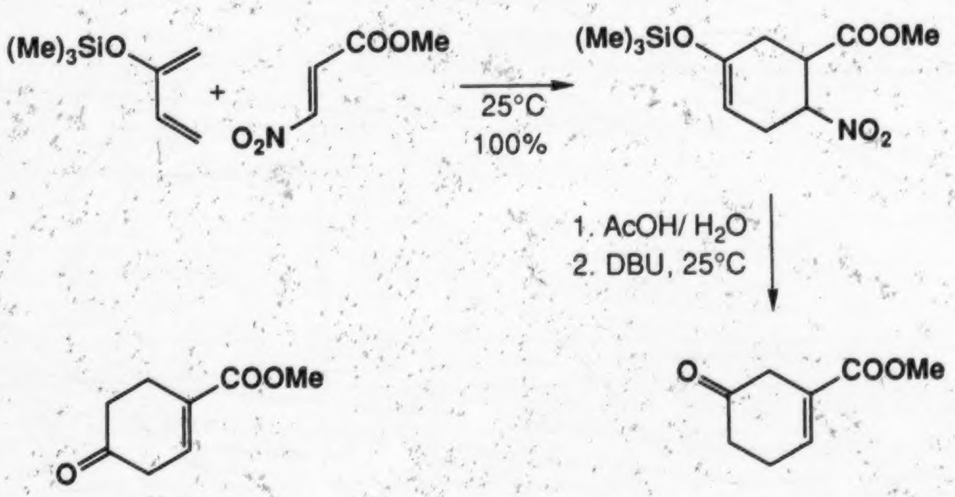
**1** **2** (18 : 1)

"*ortho*" "*meta*"



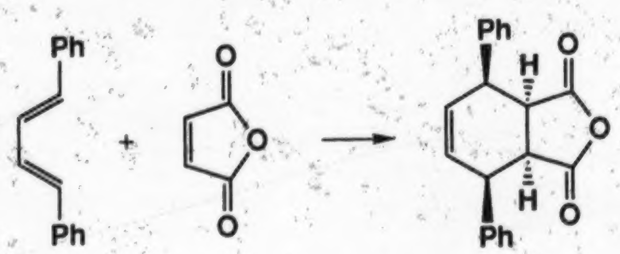
**3** **4** (5.4 : 1)

"*para*" "*meta*"



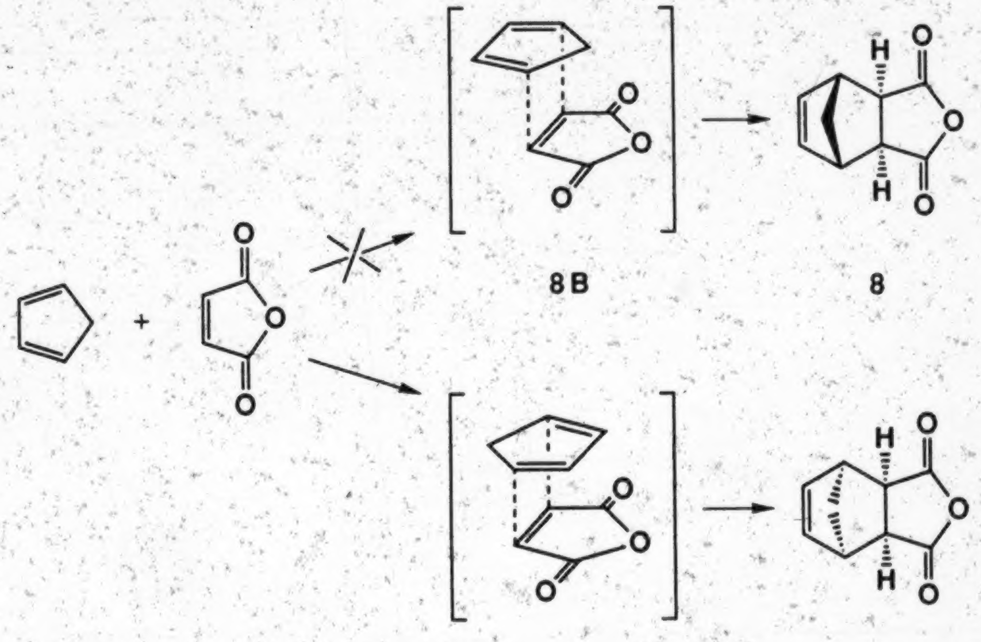
**6** **5**

The relative stereochemistry of the adduct obtained in many Diels-Alder reactions can be predicted using the empirical rules formulated by Alder and Stein in 1937.[22] According to the *cis* principle, the addition of the diene (in the cisoid conformation) and the dienophile occurs from the same face at each end of the diene moiety and both ends of the dienophilic double bond. This implies that the relative stereochemistry of the substituents in both diene and dienophile is retained in the adduct. This is illustrated by the reaction of maleic anhydride and *trans*, *trans*-1,4-diphenylbutadiene where the phenyl groups are *cis* to each other (Eqn 1).[23] The *cis* principle can be readily explained by Woodward and Hoffmann's[7] symmetry-allowed concerted [$\pi$2s + $\pi$4s] cycloaddition.



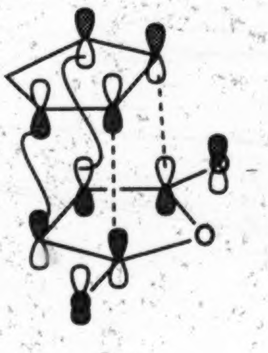
Eqn 1

In general, the addition of cyclic dienes and dienophiles can follow two possible "sandwich like" transition states (**7A** and **8B**); however, one is generally favored. According to Alder's *endo* rule, the more favored one is that with the "maximum accumulation of double bonds".[1] Not only the double bonds which actually take part in the addition are taken into account, but also the $\pi$-bonds of the activating groups in the reactants. Thus, the addition of maleic anhydride to cyclopentadiene led almost exclusively to the *endo*-adduct **7**[24] and not the *exo*-adduct **8**. This effect has been rationalized[7] as a stabilization of the *endo* transition state by secondary orbital interactions (as shown by the dashed lines in **9**).



**8B** **8**

**7A** **7**

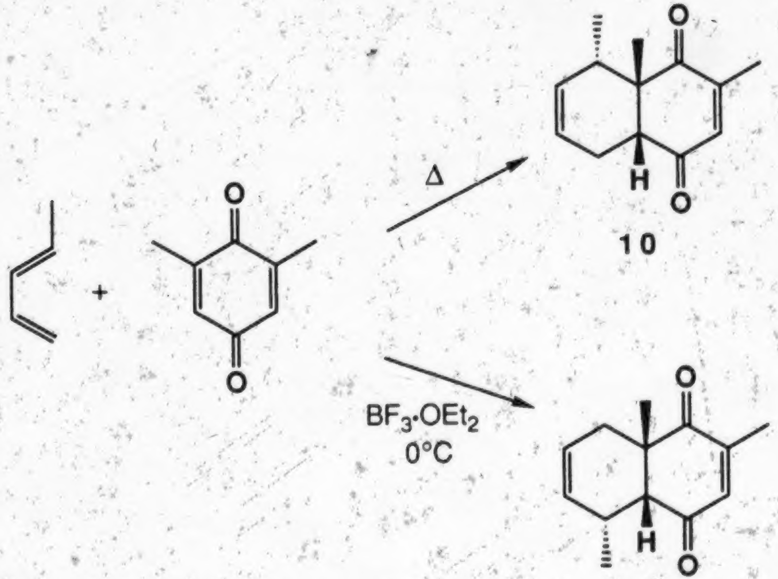


**9**

It has been found that Lewis acids such as aluminium chloride, boron trifluoride and stannic chloride produce large increases in the rate of Diels-

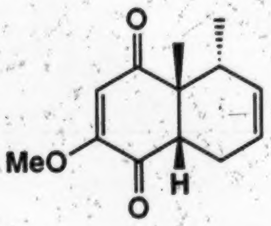
Alder reactions.[25] For example, butadiene and methyl vinyl ketone react in one hour at room temperature in the presence of stannic chloride to give a 73% yield of acetylcyclohexene. In the absence of a catalyst no adduct is formed. Furthermore, catalysis by Lewis acid can also influence the regio- and stereoselectivity of Diels-Alder reactions so that the *ortho*-[26,27] and *para*-selectivity[28-32] of the addition as well as the *endo*-selectivity[33-35] are greatly increased. On the other hand, Valenta and co-workers[36] reported a reversal of regioselectivity of Diels-Alder reactions of quinones catalyzed by Lewis acids. Thus, the thermal reaction of 2,6-dimethyls-benzoquinone with *trans*-piperylene gave **10** while the boron trifluoride etherate catalyzed reaction gave **11**. Previously it had been assumed that in a Diels-Alder reaction, the Lewis acids which increase regioselectivity would enhance the formation of the same regioisomer. It now appears that this is not the case and the orientation of the product may depend on the Lewis acid used.[37] Thus the reaction of 2-methoxy-5-methylbenzoquinone with piperylene at -16°C using stannic chloride as a catalyst, produced a 1 : 20 mixture of adducts **12** and **13**, respectively. In contrast, the same reaction catalyzed by boron trifluoride gave a 4 : 1 mixture of adducts **12** and **13**.

Recently, extensive efforts have been made to induce asymmetry in carbon-carbon bond forming reactions.[38, 39] Among these, the asymmetric Diels-Alder reaction pioneered by Walborsky[40, 41] has been established as one of the most important tools in modern asymmetric synthesis. In this pericyclic reaction, as many as four chiral centers can be created as shown

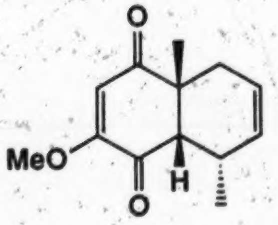


10

11

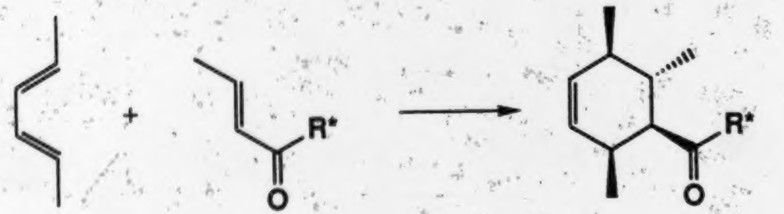


12



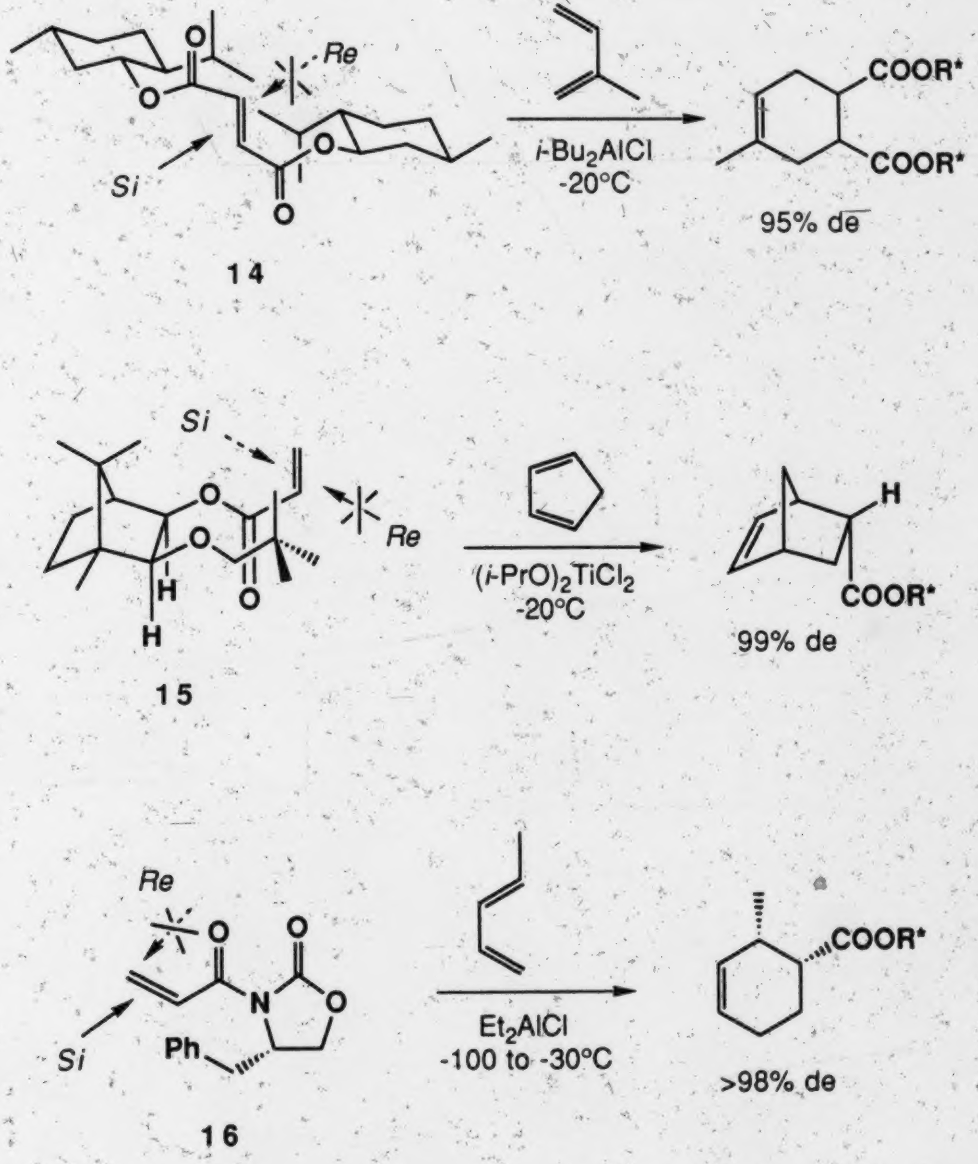
13

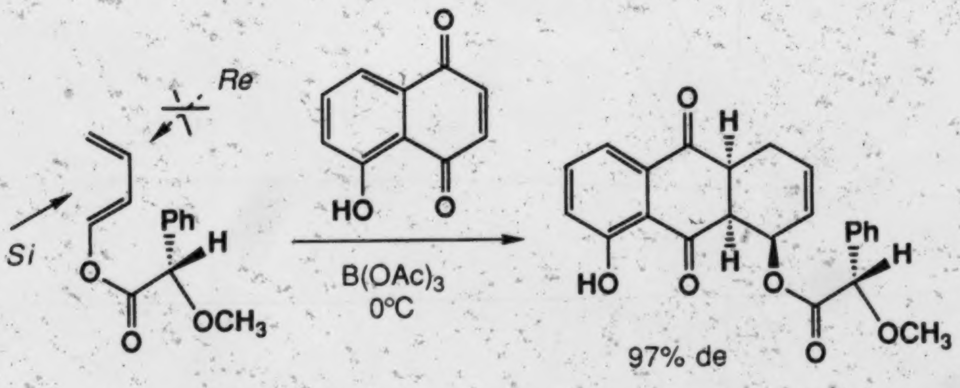
in Eqn 2. Hypothetically, $2^4 = 16$ stereoisomers can be produced. However potential stereoselection could be attained with the aid of the elements which govern the stereochemical course of the reaction, such as *cis*-addition, *endo*-addition and diastereofacial selectivities (orientation of diene and dienophile in the transition state). The majority of the work on asymmetric Diels-Alder reactions deal with optically active dienophiles[42-50] or dienes[51-53] which carry a removable chiral auxiliary group. This is exemplified by Scheme 1, in which compounds **14-17** undergo Diels-Alder reactions in the presence of a Lewis acid catalyst with diastereoselection exceeding 90%. They were devised in such a way that the chiral auxiliary group effectively blocked the *Re*-face of the dienophiles or diene and this induced high diastereofacial selectivities. Some of the chiral auxiliaries are crystalline, inexpensive and readily available from naturally occurring monoterpenes, hydroxy acids, amino acids and sugars. Compared to the use of a covalently attached chiral auxiliary group, the use of a chiral catalyst appears to be a potentially more attractive method to achieve asymmetric Diels-Alder reactions of prochiral dienes and dienophiles as two synthetic steps could be avoided. However, the attempted use of chiral Lewis acids such as menthoxyaluminium dichloride,[54] cyclohexanol derivatives of alkoxyaluminium dichloride,[55] Eu(hfc)$_3$,[56] acyloxyborane[57] and alkoxy titanium(IV) reagents[58, 59] gave variable results. Only the chiral titanium reagents afforded greater than 90% asymmetric induction.



Eqn 2

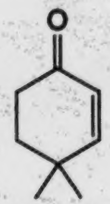
**Scheme 1**


Re
Si
14
$i$-Bu$_2$AlCl
-20°C
COOR*
COOR*
95% de
Si
Re
H
H
15
($i$-PrO)$_2$TiCl$_2$
-20°C
H
COOR*
99% de
Re
Si
Ph
16
Et$_2$AlCl
-100 to -30°C
COOR*
>98% de

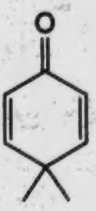


**17**

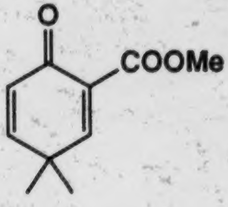
In principle, the addition of substituted cyclohexenones to a substituted 1,3-butadiene is a versatile approach to octalin systems. However, the thermal cycloaddition of dienes to cyclohexenones requires drastic conditions and produces low yields of the adduct.[60] In recent years, greater understanding of the steric and electronic effects governing this reaction and the use of Lewis acid catalysts has led to the utilization of specifically functionalized dienes and dienophiles to produce previously unattainable substitution patterns regio- and stereoselectively. Wenkert and co-workers[61-65] have made an extensive study of the Diels-Alder reaction of cycloalkenones using $AlCl_3$ as a catalyst. Liu and Browne[66-69] carried out an extensive study of the Diels-Alder reactions of the 4,4-dimethyl-2-cyclohexen-1-ones **18**-**20**. They observed improved reaction rates and yields by the introduction of an additional electron-withdrawing group into the dienophilic moiety (**20**) as predicted by Alder's rule.[14, 70] That study also indicated the potential of using different Lewis acid catalysts to effect different regiochemical outcomes in the reaction of isoprene with dienone **20**.[68] Thus, in the addition of isoprene to **20** in ether, at room temperature, boron trifluoride etherate catalysis gave adducts **21** and **22** in a ratio of 30 : 70. On the other hand, the use of stannic chloride as a catalyst produced an 82 : 18 ratio of adducts **21** and **22**. The formation of the abnormal *anti-para* adduct **22** has been rationalized by a steric effect. Due to the effect of preferential coordination of the relatively hard Lewis acid (boron trifluoride etherate) with the ketone carbonyl group, transition state **A** was preferred. Since the electron withdrawing effect on the dienophilic double bond promoting *para*-rule guided addition (**21A**) was insufficient to counteract the steric directing effect which promoted *anti-para* addition (**22A**), **22** was predominantly formed rather than **21**. In the case of $SnCl_4$, the Lewis acid is capable of forming a hexacoordinated complex with β-dicarbonyl compounds. In this complex (**23**), the electron withdrawing effect of the Lewis acid acting through both carbonyls, led to the formation of **21** as the major product *via* **21B**. This result has led to the successful synthesis of both α- and β-himachalene by the use of adduct **21**.



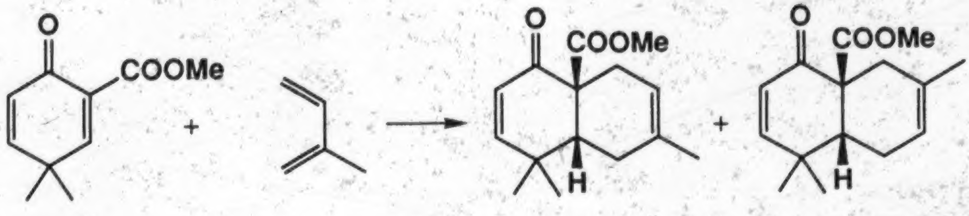
**18**



**19**

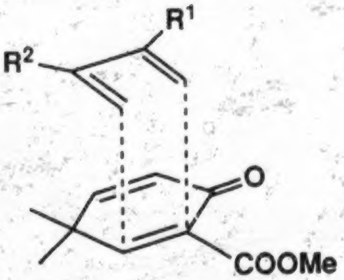


**20**



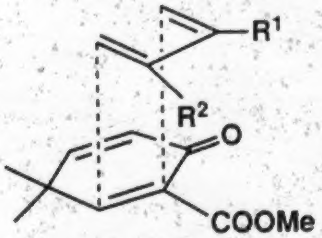
**20** **21** **22**

| | |
|---|---|
| $BF_3{\cdot}OEt_2$ | 30 : 70 |
| $SnCl_4$ | 82 : 18 |

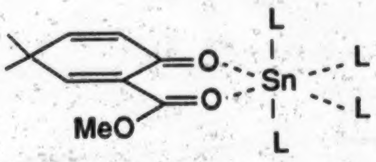


**21A** $R^1$=H, $R^2$=$CH_3$

**22A** $R^1$=$CH_3$, $R^2$=H

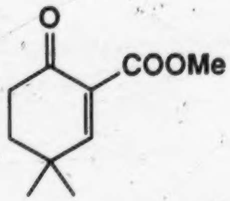


**21B** $R^1$=H, $R^2$=$CH_3$

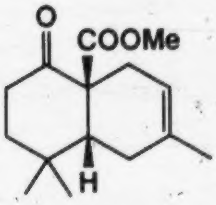


**23**

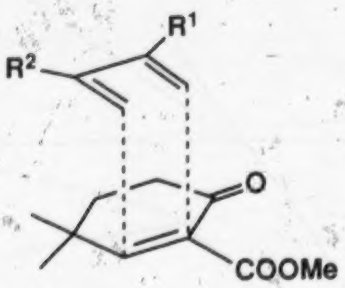
In order to study the effect of the double bond in this system, we have carried out the Diels-Alder reaction of the enone ester **24** with isoprene.[71] This was examined using three Lewis acid catalysts and a variety of reaction conditions. In all cases, the "*para*" addition product **25** was observed regardless of the choice of catalyst or temperature. The regiochemical results of these additions implied that the preference for transition state **A** having secondary orbital interaction with the ketone carbonyl observed in the addition to **20**, was not present in the additions to **24**. The difference in behavior of **20** and **24** under these reaction conditions arises from a relative reduction in secondary orbital effect stabilization of the **A** type transition state due to chemical reduction of the $C_5$-$C_6$ double bond and loss of its contribution to the cross-conjugated $\pi$-orbital system. Potential steric interaction between the quasi-axial proton of the $C_5$ methylene of **24** and the diene would also contribute to the observed effect. Most likely, these two effects combine to eliminate completely any addition by type **A** (**25A** and **26A**) transition states. Thus, the *para* addition product **25** was formed exclusively *via* transition state **25B** in which the usual directing effects are unmodified. This showed that other than catalyst selection, a remote structural feature such as the cross-conjugated double bond in this dienophile system played an important role in the regio- and stereochemical outcome of the Diels-Alder reaction.



**24**

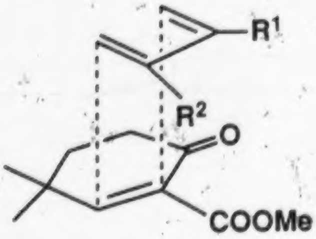


**25**



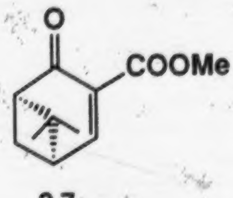
**25A** R$^1$=$CH_3$, R$^2$=H

**26A** R$^1$=H, R$^2$=$CH_3$



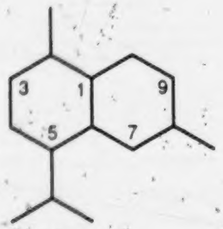
**25B** R$^1$=H, R$^2$=$CH_3$

After examining the steric and electronic effects influencing the regiochemistry of Diels-Alder reactions of enone ester **24**, we were interested in investigating further the steric influence on the diastereofacial selectivity of Diels-Alder reactions of enones. The stereofacially differentiated dienophile **27** was chosen for this purpose. A series of Diels-Alder reactions of **27** and various dienes using different Lewis acid catalysts under different reaction conditions were carried out. It showed that dienophile **27** could be a useful chiral reagent for Diels-Alder based synthetic schemes. The synthetic potential of the dienophile **27** is illustrated by strategic application to the synthesis of chiral cadinane sesquiterpenes.

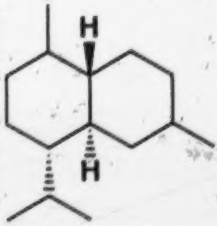


**27**

Cadinenes and other related sesquiterpenes with carbon skeleton **28** occur frequently in nature and have been further divided into four classes of compounds based on the nature of the ring fusion and the orientation of the isopropyl group at C$_5$. The four classes are the cadinanes **29** (*trans*, *trans* relative stereochemistry of 1-H, 6-H and 5-H), muurolanes **30** (*cis*, *trans*), amorphanes **31** (*cis*, *cis*) and the bulgaranes **32** (*trans*, *cis*).[72] Due to the complex stereochemistry of the sesquiterpenes belonging to these classes, structure determination is a challenging task.[72, 73] Errors in structure assignment are not unprecedented.[74-76] In 1984, ten new sesquiterpene acids (parent to esters **33-42**) were isolated from the plant *Leucanthermopsis pulverulenta*, the structures of which were assigned by a combination of spectral evidence and chemical correlation with 2-β-hydroxy-α-cadinol, **43**.[77]

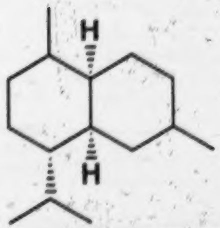


**28**



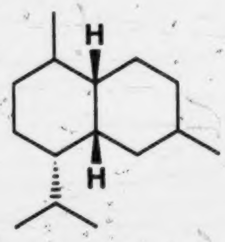
**29**

Cadinane



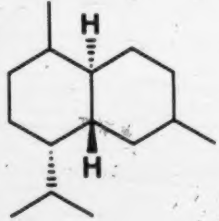
**30**

Muurolane



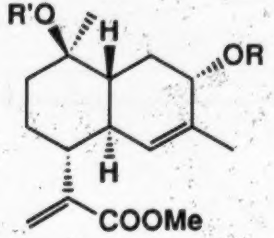
**31**

Amorphane

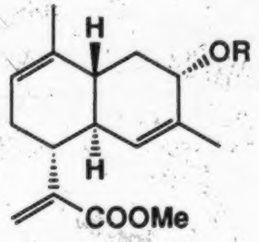


**32**

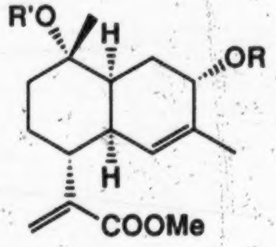
Bulgarane



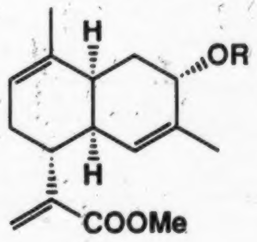
**33** R=Ac, R'=H
**34** R=H, R'=H
**35** R=Ac, R'=Et
**36** R=H, R'=Et



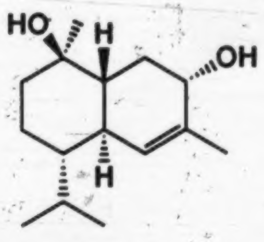
**37** R=Ac
**38** R=H



**39** R=Ac
**40** R=H

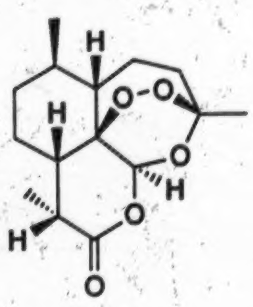


**41** R=Ac
**42** R=H

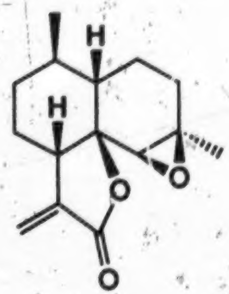


**43**

In 1972, a highly oxygenated sesquiterpene peroxide, **44** was isolated from the Chinese medicinal plant Qinghao (*Artemisia annua* L.).[78] Since ancient times Qinghao has been used for the treatment of malaria in China and its active crystalline constituent **44** was isolated from the aerial portion of this plant in 0.01-0.5% yield by an as yet unpublished procedure. Chinese investigators named the crystalline compound qinghaosu (meaning "active principle of Qinghao"), arteannuin or "artemisinine". Because the material is a terpene, rather than an alkaloid or amine, which the "ine" suffix suggests, the name "artemisinin" is preferred by Chemical Abstracts.[79] (+)-Artemisinin was also isolated from *Artemisia annua* collected in the United States.[80] Its unusual tetracyclic structure and absolute stereochemistry have been established by combined spectral, chemical and X-ray crystallographic methods.[78, 81] The *trans* configuration of the lactone ring was arrived at by comparison of its ORD spectrum[78] with that of artennuin B (**45**), a structurally related sesquiterpene isolated from *A. annua* in Yugoslavia. (+)-Artemisinin has direct parasiticidal action on *Plasmodium* in the erythrocytic stage and effects *Plasmodium vivax* and chloroquine-resistant *falciparum* malaria. In 1979, the Qinghaosu Antimalaria Coordinating Reseach Group reported the treatment of 2099 malaria patients (*P. vivax* and *P. falciparum* in a ratio of about 3 : 1) with different dosage forms of (+)-artemisinin. It was found to be both fast acting and effective against these strains of malaria. No obvious adverse reactions or noticeable side effects were observed in these patients.[79] However, compared with chloroquine, the disease treated with (+)-artemisinin recurred sooner than with chloroquine.[82] Toxicity studies on (+)-artemisinin showed that overall the acute toxicity of (+)-artemisinin is considerably less than that of chloroquine. The most striking results achieved with (+)-artemisinin were observed in the treatment of cerebral malaria which is an advanced form of *P. falciparum* malaria that can occur when > 5% of erythrocytes are infected with parasites. When (+)-artemisinin was administered to 106 patients with cerebral malaria, the cure rate averaged about 90%. The time for recovery from coma was approximately 21 h when the oil suspension was used. By comparison, quinine cured 97% of the patients but required about 47 h of recovery from coma.[79] Further studies of antimalarial effects against different strains of malaria have been carried out *in vitro* and *in vivo*.[83-91]

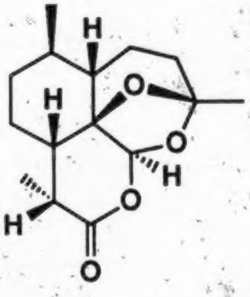


**44**

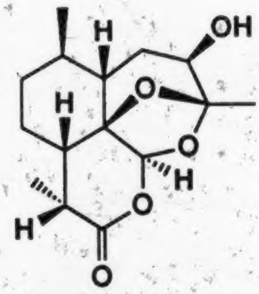


**45**

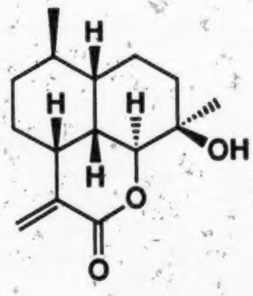
Thus far, eight other sesquiterpenes (**45-52**) have been isolated from the Chinese *Artemisia annua*.[82] They are all closely related and form the amorphane series. Testing of these sesquiterpenes which lack the peroxy group showed no antimalarial activity. Also extractions of the urine from the patients who were given (+)-artemisinin orally, with ethyl acetate, yielded four metabolites. Two of these are desoxyartemisinin (**46**) and dihydrodesoxyartemisinin (**53**). These metabolites are inactive against malaria *P. bergei* in the mouse, which showed that the peroxy function is vital for antimalarial activity.[79] (+)-Artemisinin is only sparingly soluble in water or oils and is not well absorbed by the gastrointestinal tract. A search for more potent analoques of (+)-artemisinin with better bioavailability was focussed on dihydroartemisinin (**54**) and its derivatives (**55**). Dihydroartemisinin was obtained from the sodium borohydride reduction of (+)-artemisinin.[82, 87] Three types of derivatives of dihydroartemisinin have been made (listed in order of their overall antimalarial efficacy): ethers (**55**, R=alkyl) < esters (**55**, R=CO-alkyl or -aryl) < carbonates (**55**, R=COO-alkyl or -aryl). Many of these compounds are more potent than (+)-artemisinin.[79, 87]



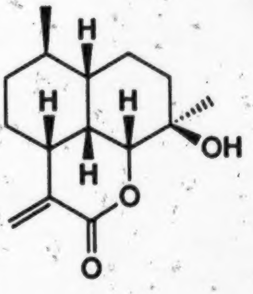
**46**



**47**



**48**



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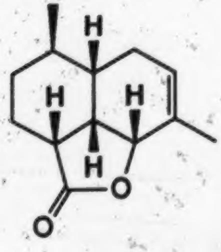
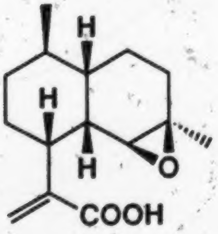
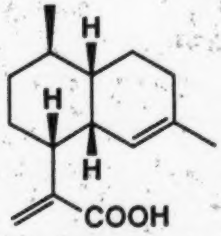


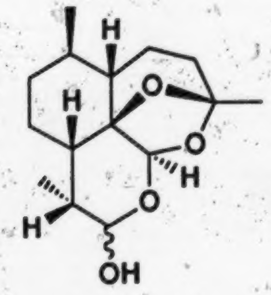
**50**



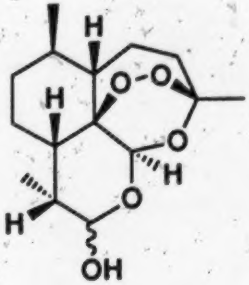
**51**



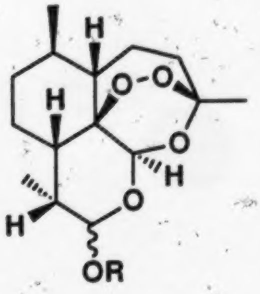
**52**



**53**



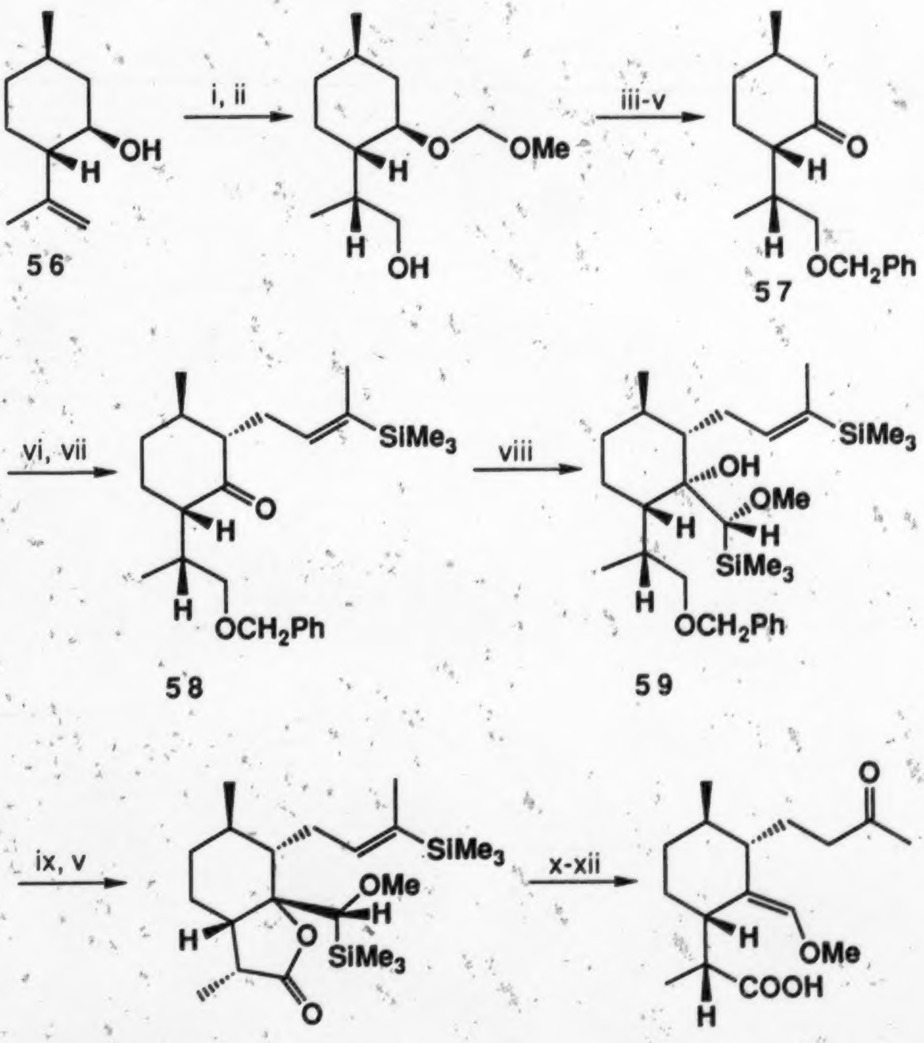
**54**

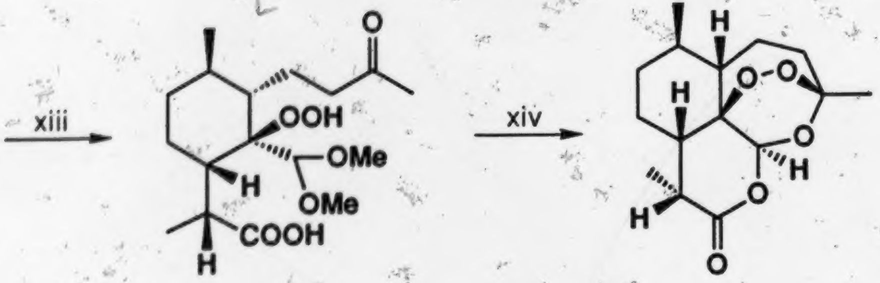


**55**

The combination of promising biological activity, the intriguing chemical structure and low natural yield (0.01-0.5%) of (+)-artemisinin **44**, has prompted four total syntheses. In these total syntheses, optically active and readily available monoterpenes were used as the starting material. In 1983, Schmid and Hofheinz[92] reported the first total synthesis of (+)-artemisinin (Scheme 2), they began their construction of the molecule with (-)-isopulegol **56** (with two required chiral centres). The key steps included the conversion of (-)-isopulegol **56** into the menthone derivative **57**, followed by the stereoseletive steps to **58** and **59**. The high stereoselectivity in the conversion of **58** to **59** could only be achieved by using a ten fold excess of lithium methoxy(trimethylsilyl)methylide, as a result of kinetic resolution of the racemic organolithium reagent by the chiral ketone **58**. The penultimate step (the photooxygenation reaction) depended both on the temperature and the solvent used. A complex mixture in methanol was obtained at -78°C. It was assumed that the major product must have been **60**, since treatment of the crude product with formic acid gave (+)-artemisinin in 30% yield, identical in every respect with the natural product.

### Scheme 2



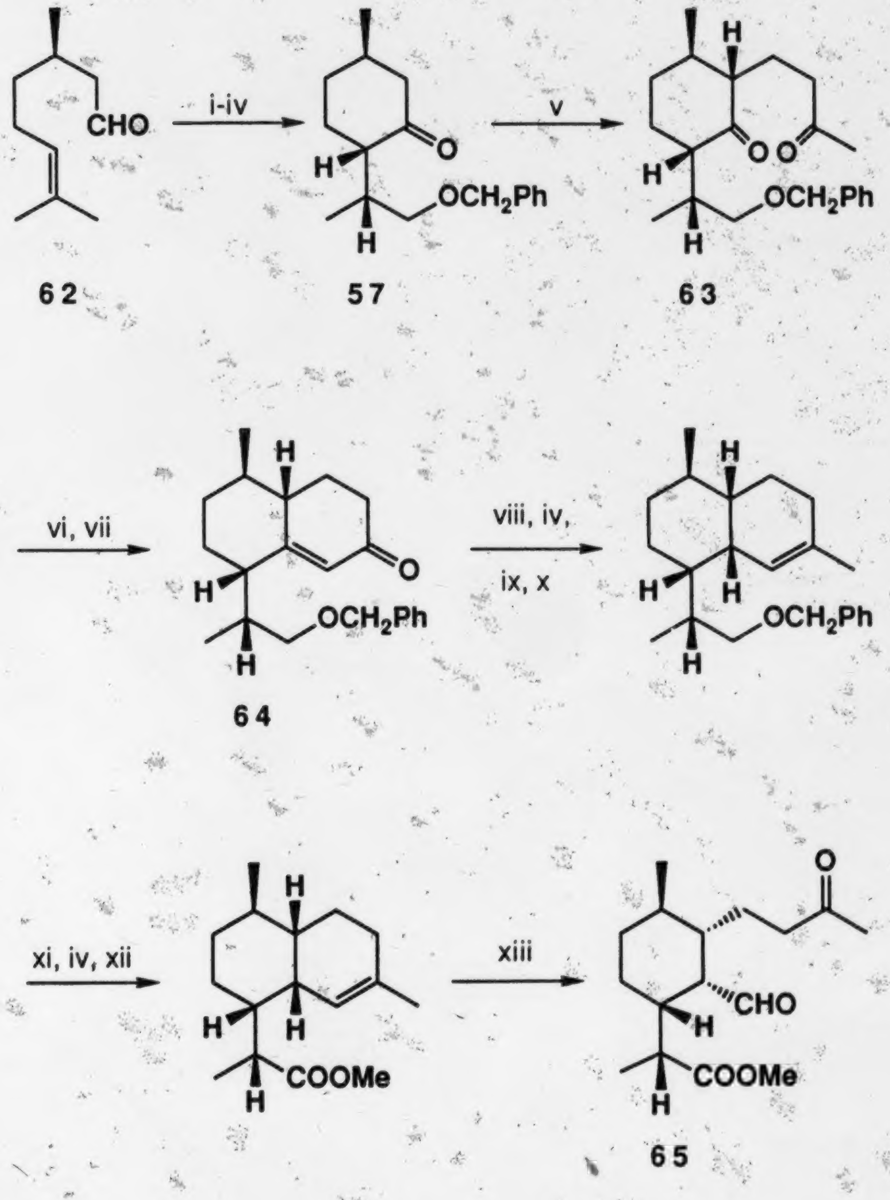


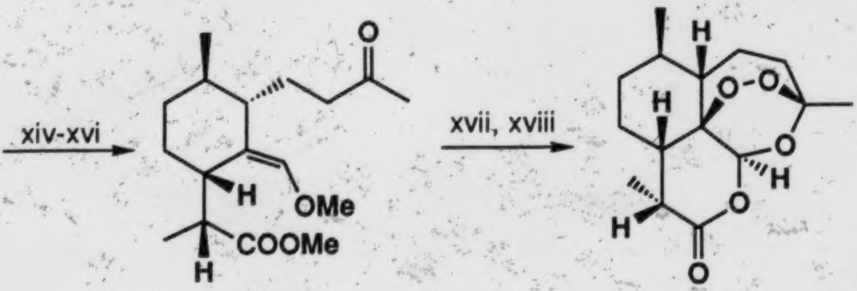
**60** **44**

Reagents: (i) $ClCH_2OMe$, $PhNMe_2$; (ii) $B_2H_6$, $OH^-$, $H_2O_2$; (iii) $PhCH_2Br$, KH; (iv) MeOH, HCl; (v) $C_6H_5NH^+ClCrO_3^-$; (vi)$LiNPr_2$; (vii) $ICH_2CH{=}C(SiMe_3)Me$; (viii) $MeOCH(Li)SiMe_3$; (ix) Li, $NH_3$; (x) $ClC_6H_4CO_3H$; (xi) $CF_3CO_2H$; (xii) $Bu_4NF$; (xiii) $^1O_2$, -78°C, MeOH; (xiv) $HCO_2H$.

In 1986, Zhou and co-workers[93] also developed a total synthesis of (+)-artemisinin. The key intermediate **61** was obtained from (R)-(+)-citronellal **62** through the reaction sequence outlined in Scheme 3. (R)-(+)-citronellal was converted to the menthone derivative **57** (the same intermediate as Schmid and Hofheinz) followed by stereoselective alkylation to give **63**. In the cyclization reaction of **63**, inversion of configuration of the isopropenyl group occurred readily when a strong base (sodium hydroxide) was used. When **63** was treated with barium hydroxide followed by 2.5% oxalic acid, ketone **64** was obtained. After introduction of the vinyl methyl group, the carbon-carbon double bond was cleaved by ozonolysis to give **65** which was subsequently converted to the key intermediate **61**. Using the same approach as Schmid and Hofheinz, the hydroperoxide moiety was introduced in **61** by photooxidation with singlet oxygen followed by acid treatment.

Scheme 3


CHO
62
i-iv
O
H
OCH₂Ph
H
57
v
H
O
O
H
OCH₂Ph
H
63
vi, vii
H
O
H
OCH₂Ph
H
64
viii, iv,
ix, x
H
H
H
OCH₂Ph
H
xi, iv, xii
H
H
H
COOMe
H
xiii
O
CHO
H
COOMe
H
65

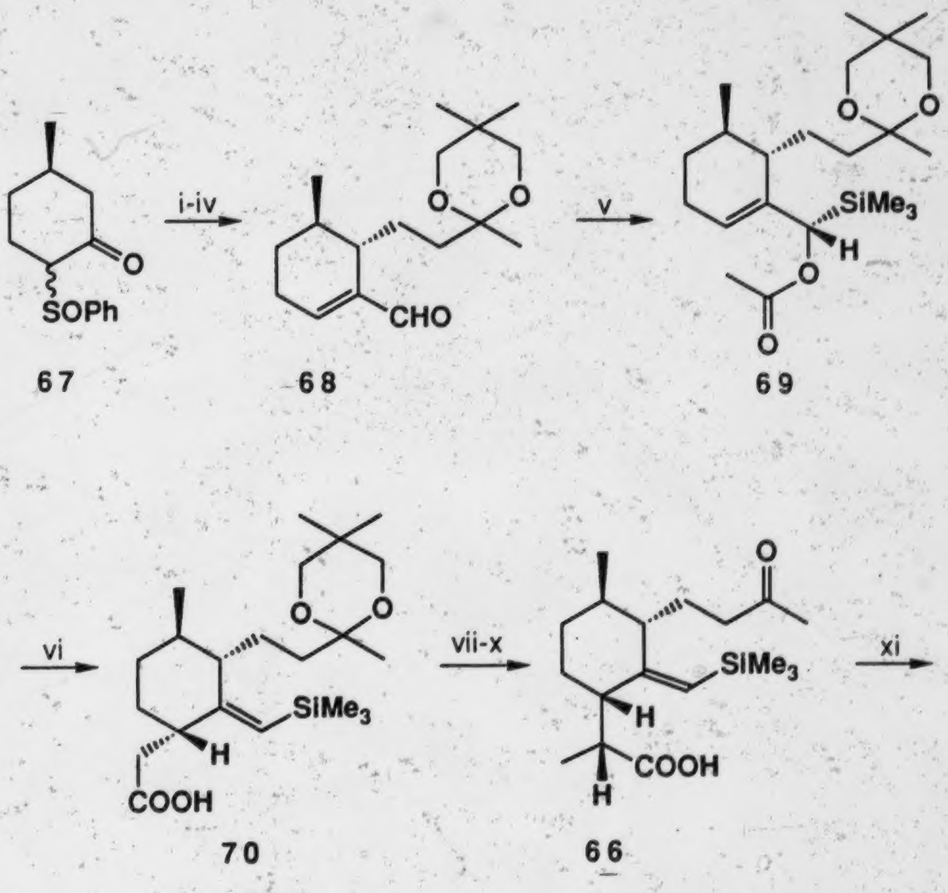


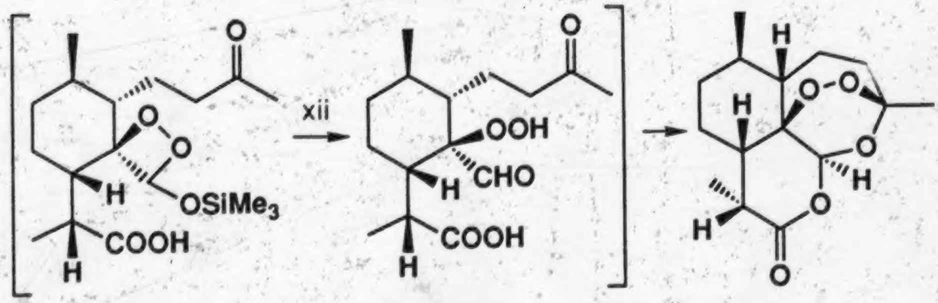
**61** **44**

Reagents: (i) $ZnBr_2$; (ii) $B_2H_6$, $OH^-$, $H_2O_2$; (iii) $PhCH_2Cl$, NaH; (iv) Jones oxidation; (v) LDA, $CH_2{=}C(SiMe_3)COCH_3$; (vi) $Ba(OH)_2{\cdot}8H_2O$; (vii) $(CO_2H)_2$; (viii) $NaBH_4$; (ix) MeMgBr; (x) p-TsOH; (xi) Na, $NH_3$; (xii) $CH_2N_2$; (xiii) $O_3$; $Me_2S$; (xiv) $HS(CH_2)_3SH$, $BF_3{\cdot}OEt_2$; (xv) $HC(OMe)_3$, p-TsOH; xylene, Δ; (xvi) $HgCl_2$; (xvii) $^1O_2$; (xviii) 70% $HClO_4$.

In 1987, Avery *et al.*[94] reported a different approach to the total synthesis of (+)-artemisinin. This synthesis differed from the previous two in that the chiral centre of the isopropenyl group was introduced by an Ireland-Claisen rearrangement instead of directly from the starting material and the hydroperoxide was introduced by exposure of vinylsilane to ozone. The required keto-acid cyclization substrate **66** was prepared in the optically active form according to Scheme 4. The known 3R chiral sulfoxide **67** was converted to aldehyde **68**. Diastereoselective addition of tris(trimethylsilyl) aluminium etherate to **68** followed by the addition of acetic anhydride and 4-dimethylaminopyridine (DMAP) to the reaction mixture produced the diastereomerically pure silyl-acetate **69**. The silyl-acetate **69**, when treated with lithium *N*-isopropylcyclohexylamide afforded the acid **70** as the exclusive Ireland-Claisen ester enolate rearrangement product. Compound **70** was subsequently converted to the key intermediate **66**. In the final key step, the hydroperoxide was introduced by treatment of **66** with ozone followed by acid. This step involved the ring opening of a transient silyloxydioxetane **71** to a labile α-hydroperoxy aldehyde **72**, which underwent further selective cyclization to **44**.

**Scheme 4**



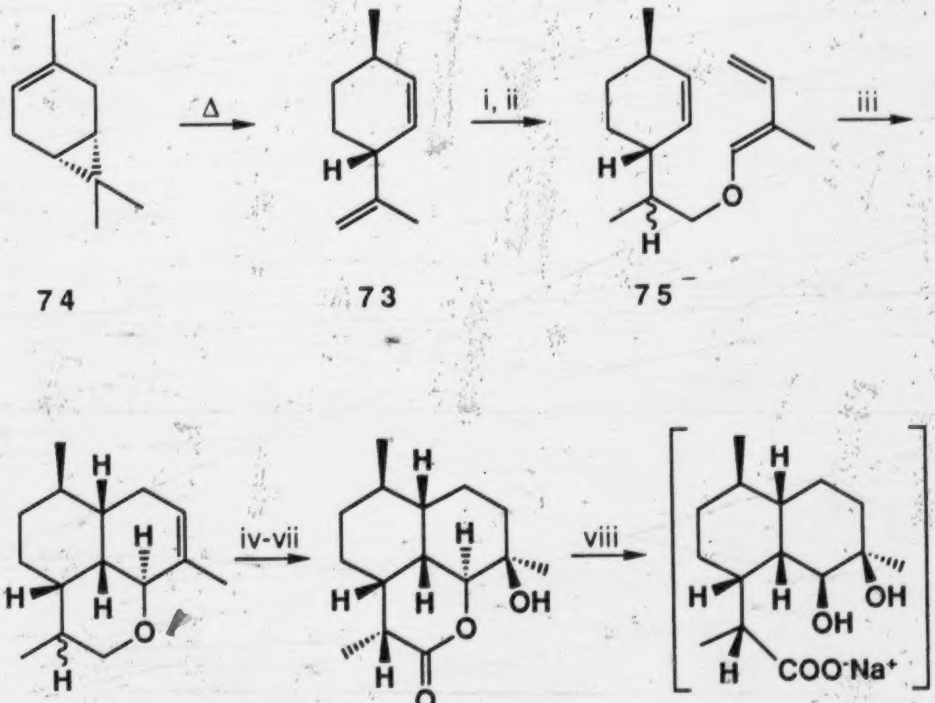


**71** **72** **44**

Reagents: (i) 2.2 eq LDA, 2-(2-bromoethyl)-2,5,5-trimethyl-1,3-dioxane; (ii) Al(Hg); (iii) $NH_2NHTs$; (iv) 4 eq *n*-BuLi, DMF; (v) $(Me_3Si)_3Al{\cdot}OEt_2$; $Ac_2O$; (vi) LICA; (vii) $Me_2SO_4$, $K_2CO_3$; (viii) LICA, MeI; (ix) KOH, MeOH; (x) $(CO_2H)_2$, silica gel; (xi) $O_3$; (xii) $CF_3CO_2H$.

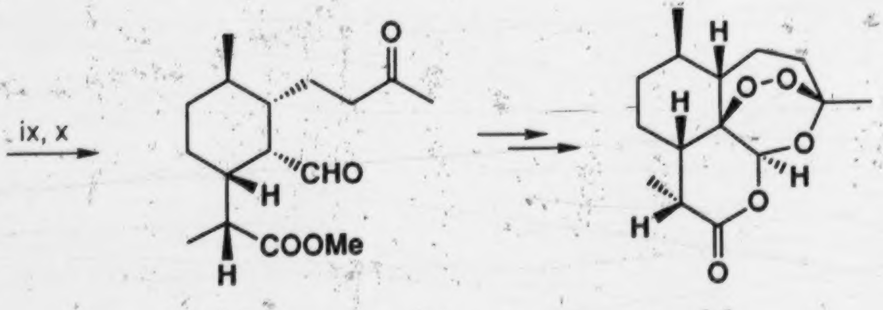
A stereoselective synthesis of (+)-artemisinin *via* an intramolecular Diels-Alder reaction was developed by Ravindranathan and co-workers[95] (Scheme 5). The starting material was (+)-isolimonene **73** which in turn could be easily derived from (+)-3-carene **74**, a cheap and readily available monoterpene. Regioselective hydroboration of **73** afforded the primary alcohol, which was converted to the enol ether **75** by transetherification. The intramolecular Diels-Alder reaction of **75** in toluene containing a small amount of pyridine and a catalytic amount of hydroquinone on heating in a sealed tube at 210°C for 72 h gave **76**. Molecular model studies on **75** revealed that the diene approaches the dienophile from the α-side only and in an *exo* orientation resulting in a β-orientation of the ring junction protons. Compound **76** was further converted to lactone **77** which was saponified with sodium hydroxide. The resultant carboxylate anion **78** was cleaved and esterified to give the keto-aldehyde **65** which was identical in its spectral properties with those reported by Zhou. Since the conversion of the keto-aldehyde **65** to artemisinin was reported earlier, this work constitutes a formal total synthesis of (+)-artemisinin.

**Scheme 5**



74 73 75

76 77 78



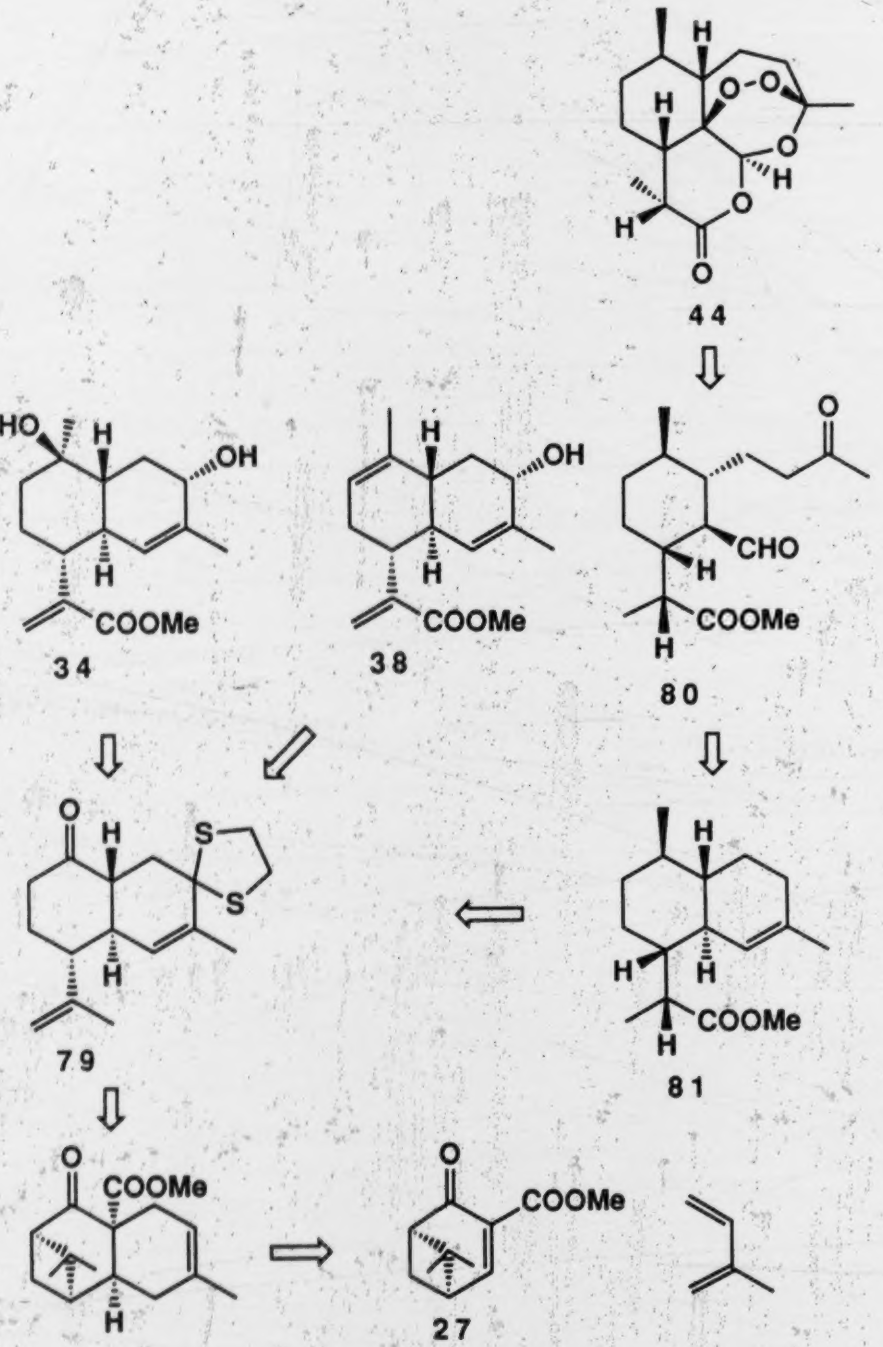
65

44

Reagents: (i) 1 eq 9BBN; NaOH, $H_2O_2$; (ii) 1-ethoxy-2-methyl-1,3-butadiene, $Hg(OAc)_2$, NaOAc; (iii) 210°C, sealed tube; (iv) $ClC_6H_4CO_3H$; (v) $LiAlH_4$; (vi) $RuCl_3{\cdot}H_2O$, $NaIO_4$; (vii) NaOMe, MeOH; (viii) NaOH; (ix) $NaIO_4$; (x) $CH_2N_2$.

We were interested in the synthesis of sesquiterpenes and (+)-artemisinin, as the Diels-Alder reaction of **27** with isoprene would provide the required carbon skeleton after cleavage of the cyclobutane ring. Functional group modifications of **79** would then lead to the sesquiterpenes, **34** and **38** (Scheme 6). It was observed that the approach developed by Zhou and Ravindranathan involved the cleavage of a C=C bond of an amorphane carbon skeleton, we envisaged that we could also apply this strategy in our synthetic approach. Thus, the key intermediate **80** required to form (+)-artemisinin could be obtained from the cleavage of C=C bond of **81**. The results of the investigation of the Diels-Alder reaction of dienophile **27** and its application in the synthesis of sesquiterpenes and (+)-artemisinin will be dicussed in the next section of the thesis.

**Scheme 6**


H
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CHO
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80
O
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S
S
H
79
H
H
H
COOMe
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81
O
COOMe
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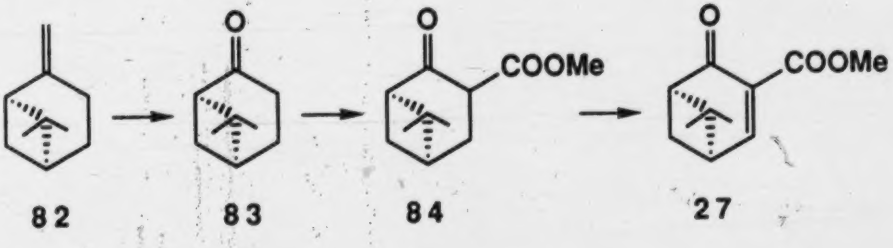
O
COOMe
27

# RESULTS AND DISCUSSION

## I. DIELS-ALDER REACTIONS OF ENONE ESTER 27

Enone ester **27** was chosen to study the effects of steric influence on Diels-Alder reactions. As this study was beginning, a single example of a Diels-Alder addition of a symmetrical diene to the corresponding ethyl ester of **27** was reported.[96] However, this report did not explore the use of Lewis acid catalysis nor the influence of stereochemical and electronic factors on the addition. Enone ester **27** could be prepared in high yield from (-)-β-pinene (**82**) in three steps (Scheme 7). (-)-β-Pinene has been used as an inexpensive, chiral starting material for chiral syntheses and the preparation of chiral reagents.[97-102] Commercial (-)-β-pinene which was obtained from the Aldrich Chemical Co. had an optical purity of 92%.

**Scheme 7**

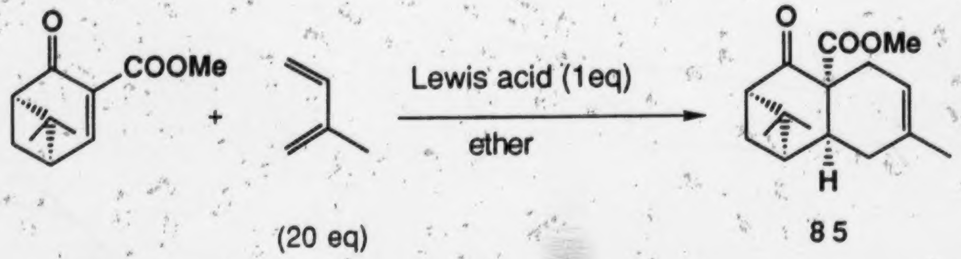


The ozonolysis of (-)-β-pinene at -78°C in a 1 : 1 mixture of dichloromethane-methanol followed by reduction of the products of ozonolysis with dimethyl sulfide gave (+)-nopinone (**83**) in 78% yield.[99] It was purified by flash chromatography on silica gel and displayed a specific rotation of $[\alpha]_D^{23}$ +16.5° (neat), which was in close agreement with the literature value.[101, 103, 104] Problems in the synthesis of (+)-nopinone have been reported. In one case, the attempted purification of (+)-nopinone by vacuum distillation resulted in an explosion.[105] Similarly, allowing the concentrated reduction mixture to warm up from 0°C to room temperature also produced or resulted in a violent explosion.[106] Because of the risk of explosion, it is recommended that researchers exercise appropriate caution when attempting this synthesis.

The carbomethoxy group was introduced by treating (+)-nopinone with sodium hydride and dimethyl carbonate in refluxing 1,2-dimethoxyethane. After heating for 6 h, keto ester **84** was obtained in 94% yield. Its spectral data (IR and $^1H$ NMR) are identical to those previously reported[101] for the same compound.

The dehydrogenation of keto ester **84** was carried out according to the method developed by Liotta *et al.*[107] Keto ester **84** was treated with phenylselenenyl chloride pyridine complex in dichloromethane. After an aqueous extraction of the reaction mixture to remove pyridine, the resulting selenide was oxidized with a 30% aqueous hydrogen peroxide solution to give the required enone ester **27** in 88% yield. Enone ester **27** showed a specific rotation of $[\alpha]_D^{23}$ +229.83° (c. 1.15, $CHCl_3$) and its IR spectrum showed carbonyl bands at 1747, 1714 and 1698 cm$^{-1}$, characteristic of $\alpha,\beta$-unsaturated keto esters. The $^1H$ NMR spectrum showed a doublet of doublets at $\delta$ 8.40 for the vinylic proton. The presence of the double bond was confirmed by signals at δ 165.57 and 127.93 in the $^{13}C$ NMR APT spectrum.

**Table 1**. Lewis acids catalyzed Diels-Alder additions of isoprene to enone ester **27**



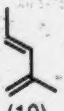
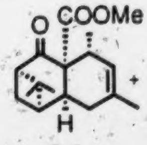
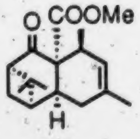
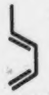
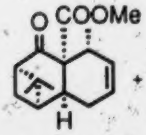
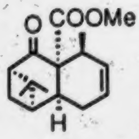
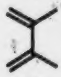
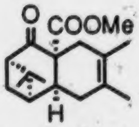
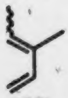
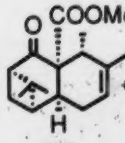
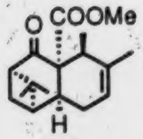
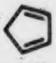
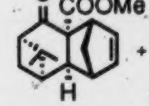
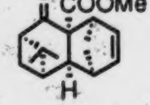
**85**

| Lewis acid | Temp (°C) | Time (h) | Yield (%) |
|---|---|---|---|
| $BF_3$·$OEt_2$ | -10 | 12 | 29 |
| $FeCl_3$ | -20 | 2.75 | 34 |
| $SnCl_4$ | 20 | 2 | 52 |
| $SnCl_4$ | -20 | 3 | 55 |
| $Et_2AlCl$ | -20 | 3 | 7 |
| $ZnCl_2$ | -20 | 21 | 95 |

A variety of conditions and Lewis acids ($BF_3$·$OEt_2$, $SnCl_4$ and $FeCl_3$) were explored for the Diels-Alder reactions of enone ester **27**. These particular Lewis acids were chosen as previously it had been noted that they were suitable as catalysts for related dienophiles. However, it was found that in the present case these Lewis acids gave poor to moderate yields of Diels-Alder adducts (Table 1). For example, the reaction of enone ester **27** with isoprene catalyzed by boron trifluoride etherate gave a 29% yield of adduct **85**, while the same reaction catalyzed by stannic chloride gave about 55% yield. In addition, the reaction of enone ester **27** with *trans*-piperylene, catalyzed by stannic chloride and boron trifluoride etherate gave no Diels-Alder adduct and no starting material was recovered. Thus, the stability of **27** and the adduct **85** under various reaction conditions were examined. The adduct **85** in ether was treated with stannic chloride at room temperature. It was found to remain intact even after 26 h. On the other hand, a mixture of **27** and stannic chloride in ether at room temperature rapidly decomposed. At -20°C, however decomposition of the enone ester was not observed. Consequently, the Diels-Alder reaction of **27** with isoprene using zinc chloride, a weaker Lewis acid, was investigated. Though the reaction was slower, a high yield of adduct **85** was obtained. Subsequently, in further investigations of the scope of Diels-Alder reactions of **27**, zinc chloride was used as the Lewis acid catalyst. Under zinc chloride catalysis, good to high yields of adducts were obtained. The results of this study are summarized in Table 2.

Although it has been successfully used in Diels-Alder reactions,[108-115] the striking superiority of zinc chloride as a catalyst in this series was unexpected. From Table 1, the yields of Diels-Alder adduct **85** formed with various Lewis acids were in the order of $Et_2AlCl$ (lowest) < $BF_3{\cdot}OEt_2$ < $FeCl_3$ < $SnCl_4$ < $ZnCl_2$ (highest), which was almost exactly opposite to the general order of Lewis acidity: $BX_3 > AlX_3 > FeX_3 > SbX_5 > SnX_4 > ZnX_2$.[116] It also

**Table 2.** $ZnCl_2$ catalyzed Diels-Alder addition of dienes to enone ester **27**[a]

| Entry | Diene (eq) | Temp (°C) | Time (h) | Product(s) | (ratio) | Yield (%) |
|---|---|---|---|---|---|---|
| 1 |  (10) | -20 | 1.5 |  **91** +  **90** | (88:12) | 59 |
| 2 | | -40 | 24 | | (91:9) | 100 |
| 3 |  (10) | -20 | 109 |  **93** +  **92** | (86:14) | 77 |
| 4[b] | | -20 | 55 | | (100:0) | 58 |
| 5 |  (20) | -20 | 41 |  **94** | | 93 |
| 6[c] |  (20) | -20 | 88 |  **95** +  **96** | (81:19) | 84 |
| 7 |  (20) | -20 | 61 |  **97** +  **98** | (89:11) | 53 |

[a] Unless otherwise specified, reactions were carried out in ether using 1 eq of $ZnCl_2$.

[b] 2 eq of $ZnCl_2$ was used.

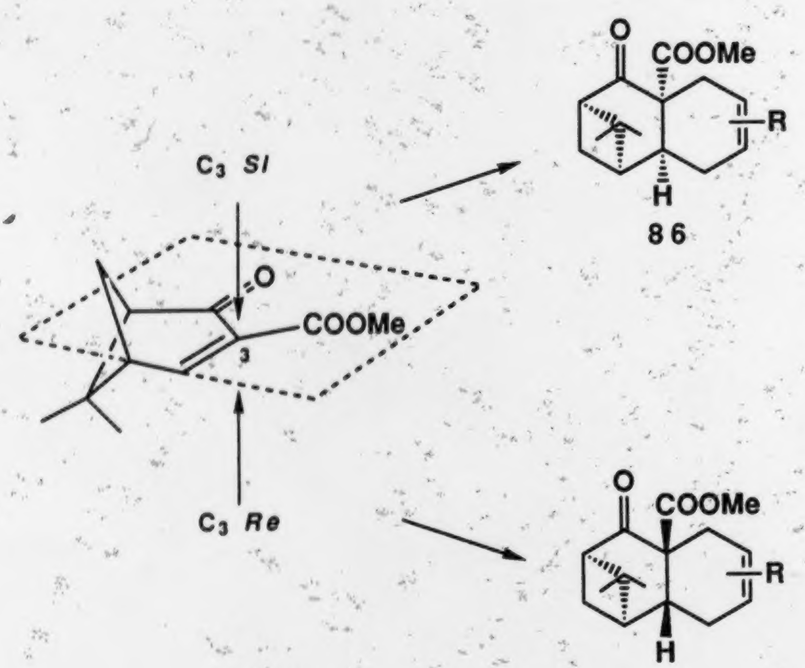
[c] A 3 : 7 mixture of *cis*- and *trans*-3-methyl-1,3-pentadiene was used.

appeared that in general the stronger the Lewis acid used the lower the yield. This may be the result of greater stability of the strained ring system of the reactant and products to the relatively mild acid condition of zinc chloride catalysis than that of the stronger Lewis acids examined.

The zinc chloride used in the Diels-Alder reactions was dried either by a flame or under vacuum, before dissolving it in ether to make a clear ethereal solution. This ethereal zinc chloride solution, followed by the diene was added to a solution of enone ester **27** at the stated temperature. When the zinc chloride solution was added, a thick white precipitate formed and the progress of the reaction was monitored by the disappearance of this precipitate. The formation of this precipitate was most probably due to the formation of a complex between zinc chloride and **27**. However attempts to recrystallize this white precipitate were unsuccessful, as it decomposed at room temperature or when it was exposed to air.

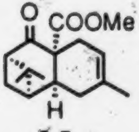
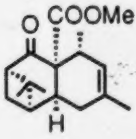
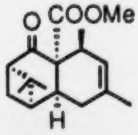
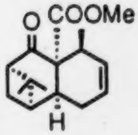
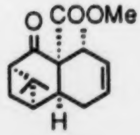
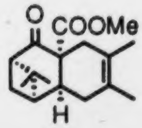
The experimental procedure for zinc chloride catalyzed reactions was slightly different to that for stannic chloride, ferric chloride and boron trifluoride etherate. Zinc chloride is only slightly soluble in ether and requires a comparatively large amount of ether to dissolve it completely. In order to keep the concentration of **27** in the reaction mixture constant, the zinc chloride solution was introduced before the diene whereas for stannic chloride, ferric chloride, and boron trifluoride etherate catalyzed reactions, the diene was introduced before the Lewis acid.

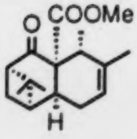
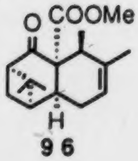
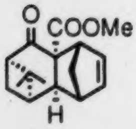
Scheme 8



In principle, Diels-Alder addition to enone ester **27** could occur from either the sterically more hindered *Re*-face or the less hindered *Si*-face to give stereochemically distinct products. In all cases only products of addition to the *Si*-face of general type **86** were obtained (Scheme 8). The *gem*-dimethyl groups in **27** served to direct the Diels-Alder addition exclusively to the less hindered *Si*-face, which was indicated by the stereochemistry of the ring junction of all the adducts. The structures of adducts were established by using spectroscopic methods including $^1$H NMR, $^1$H decoupling and NOE experiments. The results of the NOE experiments are summarized in Table 3.

**Table 3**. NOE data for Diels-Alder adducts

| Compound | Irradiation | (δ ppm) | % Enhancement (H) |
|---|---|---|---|
|  85 | *endo* $CH_3$ | (0.97) | 4.9 ($H_8$), 3.1 (*exo*$CH_3$) |
| | *exo* $CH_3$ | (1.34) | 3.9 ($H_1$), 3.4 ($H_{11}$*exo*), |
| | — | | 3.2 ($H_9$), 2.9 (*endo* $CH_3$) |
|  91 | *endo* $CH_3$ | (0.90) | 6.8 ($H_8$) |
| | $C_4$-$CH_3$ | (1.26) | 4.6 ($H_5$), 3.6 ($H_4$) |
|  90 | *endo* $CH_3$ | (0.89) | 5.6 ($H_8$) |
| | *exo* $CH_3$ | (1.32) | 4.3 ($H_1$), 3.7 ($H_{11}$*exo*) |
| | $C_4$-$CH_3$ | (1.04) | 8.5 ($H_4$), 4.6 ($H_{11}$*endo*) |
|  92 | *endo* $CH_3$ | (0.90) | 5.3 ($H_8$) |
| | $C_4$-$CH_3$ | (1.06) | 8.7 ($H_4$), 4 ($H_{11}$*endo*) |
|  93 | *endo* $CH_3$ | (0.94) | 5.7 ($H_8$) |
| | $C_4$-$CH_3$ | (1.30) | 4.7 ($H_4$), 4.7 ($H_5$) |
|  94 | *endo* $CH_3$ | (0.96) | 8.7 ($H_8$), 3.7 (*exo* $CH_3$) |

| | | | |
|---|---|---|---|
| <br>**9 5** | *endo* $CH_3$ | (0.93) | 5.9 ($H_8$) |
| | *exo* $CH_3$ | (1.33) | 4.7 ($H_1$), 2.6 ($H_9$) |
| | $C_4$-$CH_3$ | (1.23) | 6 ($H_4$) |
| <br>**9 6** | *endo* $CH_3$ | (0.82) | 4 ($H_8$) |
| | *exo* $CH_3$ | (1.34) | 4.1 ($H_1$), 3.2 ($H_{11}$*exo*) |
| | $C_4$-$CH_3$ | (1.00) | 8.4 ($H_4$), 3.8 ($H_{11}$*endo*) |
| <br>**9 7** | *endo* $CH_3$ | (0.92) | 3.0 ($H_8$) |

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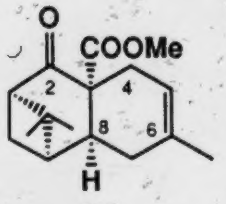
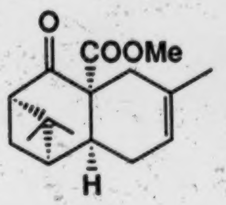
## A. Addition to isoprene

The reaction of an ethereal solution of enone ester **27** with isoprene with zinc chloride catalysis proceeded smoothly to give, in 95% yield, an adduct which displayed a specific rotation of $[\alpha]_D^{23}$ +54.2° (c. 1.12, $CHCl_3$). The $^{13}C$ NMR APT spectrum showed a set of 16 lines with 8 lines each antiphase and in phase to the deuteriochloroform signals, indicating the presence of a single compound. The mass spectrum showed a molecular ion peak at m/z 262.1516 consistent with the chemical formula $C_{16}H_{22}O_3$. The IR spectrum showed carbonyl bands at 1741, 1726 (ester) and 1710 (ketone) $cm^{-1}$. Its $^1H$ NMR spectrum displayed a multiplet at $\delta$ 5.48 for the vinylic proton, a singlet at δ 3.75 for the methoxy and three methyl singlets at δ 1.72 (vinylic), 1.34 and 0.97 (*gem* $CH_3$'s).



**85**



**87**

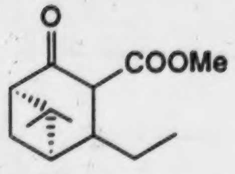
If the Diels-Alder addition followed the normal *para*-rule, then the spectral data suggest that structure **85** could be assigned to the adduct. However, orientational reversal in violation of the *para*-rule in the Diels-Alder reaction of a 2-substituted diene has been observed.[69] It was therefore possible that the addition of isoprene to enone ester **27** could produce the regioisomeric keto ester **87**. To rule out this possibility, extensive $^1H$ decoupling experiments were carried out and all the protons of the adduct were assigned. The $^1H$ NMR assignments for this compound are summarized in Table 4. A doublet of doublets, $H_{4e}$, was observed to couple to $H_5$ with a coupling constant of 6 Hz in accord with the $CH_3C{=}CH_xCH_yH$ system ($J_{xy}$ = 4-10 Hz). On the other hand, the regioisomeric adduct **87** would be expected to show a smaller coupling constant for the $CH_x{=}C(CH_3)CH_yH$ system ($J_{xy}$ = 0-3 Hz).[117] Clearly, this data in the $^1H$ NMR spectrum is consistent with the structure **85** for the Diels-Alder adduct.

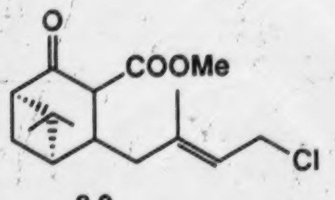
**Table 4.** $^1H$ NMR data for adduct **85**

| Proton | Chemical shift (δ ppm) | Multiplicity(*J* in Hz) |
|---|---|---|
| $H_1$ | 2.66 | dd (5.5, 5.5) |
| $H_{4e}$ | 3.05 | dd (15.5, 6) |
| $H_{4ax}$ | 2.15 | m |
| $H_5$ | 5.48 | m |
| $H_{7e}$ | 2.15 | m |
| $H_{7ax}$ | 1.87 | m |
| $H_8$ | 3.20 | dddd (8, 8, 1.5, 1.5) |
| $H_9$ | 2.15 | m |
| $H_{11exo}$ | 2.47 | dddd (11, 7, 5.5, 1.5) |
| $H_{11endo}$ | 1.95 | d (11) |
| vinylic $CH_3$ | 1.72 | br s |
| *exo* $CH_3$ | 1.34 | s |
| *endo* $CH_3$ | 0.97 | s |
| $OCH_3$ | 3.75 | s |

The stereochemistry of the ring junction was determined by NOE experiments. Irradiation of the methyl singlet at δ 0.97 resulted in 4.9% and 3.1% enhancements on $H_8$ and the methyl at δ 1.34, respectively. When the methyl at δ 1.34 was irradiated, NOE enhancements of 3.9% on $H_1$, 3.4% on $H_{11exo}$, 3.2% on $H_9$ and 2.9% on methyl at δ 0.97 were observed. This implied that $H_8$ was on the same face as the *gem*-dimethyl groups and therefore the addition of isoprene was to the *Si*-face of **27** to give adduct **85** with $\alpha$-$H_8$. On the basis of the *cis*-principle, the adduct would be expected to have an $\alpha$-carbomethoxy group. From these NOE experiments, the *gem*-dimethyl and the *exo* and *endo* protons of the methylene bridge could be assigned. The appearance of the *exo* methyl signal further down field than the *endo* methyl is probably due to the shielding of the *endo* methyl by the ketone carbonyl. The $H_{11exo}$ at $\delta$ 2.47 of dddd multiplicity, was coupled to $H_1$($J$ = 5.5 Hz), $H_9$ ($J$ = 7 Hz), $H_{11endo}$ ($J$ = 11 Hz) and $H_8$ (W-coupling, $J$ = 1.5 Hz). On the other hand, $H_{11endo}$, which was strongly shielded relative to $H_{11exo}$ appeared as a readily recognizable doublet ($J$ = 11 Hz) as the dihedral angles of $H_{11endo}$ to $H_1$ and $H_9$ were about 90°. The regiochemistry and stereochemistry of adduct **85** was further confirmed by its conversion to various cadinane sesquiterpenes.

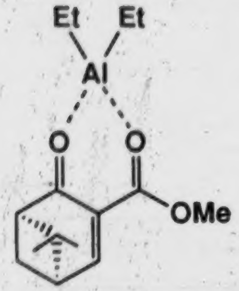
The Diels-Alder reaction of enone ester **27** with isoprene catalyzed by diethylaluminium chloride produced three compounds. The first two could not be separated and were produced in a ratio of 1 : 5 (from $^1$H NMR integration). The minor compound showed identical $^1$H NMR characteristics as **85**. The mass spectrum of the major compound showed a molecular ion peak at m/z 224.1412 which was in agreement with the formula $C_{13}H_{20}O_3$. The IR spectrum showed absorptions at 1744 (ester) and 1712 (ketone) cm$^{-1}$. The $^1$H NMR showed methyl singlets at $\delta$ 3.81 (methoxy), 1.36 and 0.97 (*gem*). It also displayed a methyl triplet at $\delta$ 0.92 and a doublet due to an $\alpha$-H of the $\beta$-keto ester at $\delta$ 3.24. This data indicated that structure **88** could be assigned to this undesired product.


**88**


**89**

The third compound showed molecular ion peaks at m/z 298.1344 and 300.1306 in the mass spectrum, which were consistent with the formula $C_{16}H_{23}O_3Cl$. The IR spectrum showed carbonyl bands at 1740 (ester) and 1711 (ketone) $cm^{-1}$. The $^1H$ NMR showed a triplet of quartets at $\delta$ 5.48 for the vinyl proton and a doublet at $\delta$ 3.24 for the $\alpha$-H of the $\beta$-keto ester. Methyl singlets appeared at $\delta$ 3.77 (methoxy), 1.36 and 0.96 (*gem*), and a doublet at $\delta$ 1.72 indicated the presence of a vinylic methyl. The presence of a double bond was confirmed by signals at $\delta$ 139.44 and 123.70 in the $^{13}C$ NMR APT spectrum. This spectrum also showed carbonyl signals at $\delta$ 207.73 and 170.59. Based on this spectral data, structure **89** could be assigned to this compound.

Compounds **88** and **89** were formed from the 1,4-addition of ethyl or isoprene respectively to the enone ester. These 1,4-additions occurred at a faster rate than the desired Diels-Alder reaction. Diethylaluminium chloride has been used as a catalyst in both Diels-Alder[49, 118, 119] and ene reactions.[120, 121] Snider reported that in ene reactions, the alkyl group of diethylaluminium chloride ($Et_2AlCl$) could act as a nucleophile and added to aldehydes to give secondary alcohols. Similarly, the ethyl could add to enone ester **27** in a Michael fashion to give compound **88**.



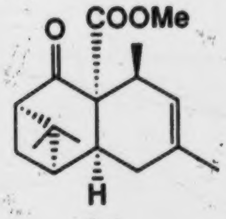
**27a**

Evans[49] reported that the influence exerted by $Et_2AlCl$ was most likely ascribed to the formation of a bidentate complex (e.g. **27a** in the present case) with β-dicarbonyl groups. During the formation of this complex, free $Cl^-$ would be liberated. The $Cl^-$ could then trap the intermediate from the Friedel-Crafts type addition of isoprene to **27** to give **89**.

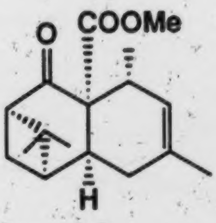
## B. Addition to *trans*-2-methyl-1,3-pentadiene

At -20°C, the zinc chloride catalyzed Diels-Alder reaction of enone ester **27** with *trans*-2-methyl-1,3-pentadiene proceeded smoothly to give a 59% yield of two adducts in a ratio of 88 : 12 (76% diastereomeric excess). These compounds were separated by flash chromatography on silica gel. The less polar minor isomer displayed a specific rotation of $[\alpha]_D^{23}$ + 145.34° (c. 0.869, $CHCl_3$) and its mass spectrum showed a molecular ion peak at m/z 276.1719 which was consistent with the formula $C_{17}H_{24}O_3$. The IR spectrum showed carbonyl bands at 1724 (ester) and 1708 (ketone) $cm^{-1}$. The $^1H$ NMR spectrum indicated the presence of a vinylic proton at δ 5.42 as a multiplet and a methoxy group at δ 3.76 as a singlet. Methyl singlets appeared at δ 1.32 and 0.89 together with a methyl doublet at δ 1.04. The presence of a double bond was confirmed by signals at δ 135.06 and 125.92 in the $^{13}$C NMR APT spectrum, which also showed carbonyl signals at δ 209.81 and 174.04.

The more polar major isomer displayed a specific rotation of $[\alpha]_D^{23}$ +27.4° (c. 1.05, $CHCl_3$) and its IR spectrum showed absorptions at 1746 and 1711 cm$^{-1}$, characteristic of the presence of an ester and a ketone. The mass spectrum showed a molecular ion peak at m/z 276.1723 corresponding to the formula $C_{17}H_{24}O_3$. The $^1$H NMR spectrum displayed a multiplet at δ 5.19 due to the presence of a vinylic proton, and a singlet at δ 3.69 due to the presence of a methoxy group. Methyl singlets occurred at δ 1.32 and 0.90 (*gem*) along with a methyl doublet at δ 1.26. The $^{13}$C NMR APT spectrum showed signals at δ 135.15 and 125.55, which confirmed the presence of a double bond. Carbonyl signals at δ 208.54 and 171.95 were also observed.



**91**



**90**

If the Diels-Alder reaction obeyed the normal *ortho-* and *para-*rules, then the structures of the two adducts could be tentatively assigned to be the keto esters **90** and **91**. To determine conclusively the regiochemistry of the

Table 5. $^1H$ NMR data for Adducts **90** and **91**

| **91**<br>δ | <br>(multiplicity; *J* in Hz) | Proton | **90**<br>δ | <br>(multiplicity; *J* in Hz) |
|---|---|---|---|---|
| 2.66 | (dd; 5.5, 5.5) | $H_1$ | 2.55 | (dd; 5.5, 5.5) |
| 2.46 | (m) | $H_4$ | 3.16 | (m) |
| 5.19 | (m) | $H_5$ | 5.42 | (m) |
| 2.27 | (dd; 16, 8) | $H_7$ | 2.15 | (m) |
| 1.91 | (br dd; 16, 8) | $H_7$ | 1.96 | (m) |
| 2.94 | (dddd; 8, 8, 2, 2) | $H_8$ | 3.25 | (dddd; 6, 6, 1.5, 1.5) |
| 2.09 | (ddd; 5.5, 5.5, 2) | $H_9$ | 1.96 | (m) |
| 2.46 | (m) | $H_{11exo}$ | 2.44 | (dddd; 11, 5.5, 5.5, 1.5) |
| 1.82 | (d; 11) | $H_{11endo}$ | 1.87 | (d; 11) |
| 1.26 | (d; 7) | $H_{12}$ | 1.04 | (d; 7.5) |
| 1.76 | (br s) | $H_{13}$ | 1.77 | (br s) |
| 1.32 | (s) | *exo* $CH_3$ | 1.32 | (s) |
| 0.90 | (s) | *endo* $CH_3$ | 0.89 | (s) |
| 3.69 | (s) | $OCH_3$ | 3.76 | (s) |

adducts, extensive $^1H$ decoupling experiments were carried out on the major isomer and a complete spectral assignment was achieved (Table 5). The ring junction proton, which appeared as a dddd at δ 2.94 ($H_8$), was coupled to $H_{7ax}$ ($J = 8$ Hz), $H_{7e}$ ($J = 8$ Hz), $H_9$ ($J = 2$ Hz) and $H_{11exo}$ (W-coupling, $J = 2$ Hz). This coupling pattern indicated that two hydrogens were attached to $C_7$. This feature was also observed in adduct **85**, in which there was no substituent at $C_7$. Thus the methyl substituent could only be located on $C_4$. The regiochemistry of the minor isomer was assigned on the basis of its $^1H$ NMR spectrum which also showed a dddd ($J = 6, 6, 1.5, 1.5$ Hz) at $\delta$ 3.25 for $H_8$. Thus the Diels-Alder adducts were found to possess the regiochemistry depicted by structures **90** and **91**.

The stereochemistry of adducts **90** and **91** remained to be determined. The two adducts could be epimeric to each other, as a result of the addition *via* secondary stabilization by the ester group or the ketone carbonyl with complete diastereofacial selectivity. On the other hand, they could be diastereomers resulting from the addition of the diene to the *Re*- or *Si*-face of the enone ester. The stereochemistry of adducts **90** and **91** was determined by NOE experiments. Irradiation of the *endo* methyl at $\delta$ 0.89 of the minor isomer resulted in an NOE enhancement of 5.6% for $H_8$. Similarly, saturation of the *endo* methyl at $\delta$ 0.90 of the major isomer produced a 6.8% NOE enhancement on $H_8$. This indicated that the addition of *trans*-2-methyl-1,3-pentadiene occurred exclusively from the *Si*-face, and adducts **90** and **91** were epimeric to each other at $C_4$. Irradiation of the methyl doublet ($\delta$ 1.26) of the major isomer resulted in an NOE enhancement of 4.6% on $H_5$ ($\delta$ 5.19) and 3.6% on $H_4$ ($\delta$ 2.46) while saturation of the methyl doublet ($\delta$ 1.04) of the minor isomer gave rise to 8.5% and 4.6% NOE enhancements on $H_4$ ($\delta$ 3.16) and $H_{11\mathit{endo}}$ ($\delta$ 1.87), respectively (see Figure 1). Evidently the $C_4$-methyl of the minor isomer is on the same face as the bridge methylene group. These experiments conclusively established the stereochemistry of the major adduct as **91** and the minor adduct as **90**.

When the zinc chloride catalyzed reaction of **27** and *trans*-2-methyl-1,3-pentadiene was carried out at -40°C, a slight increase in stereoselectivity from 76% to 82% diastereomeric excess (de) in favor of **91** was observed. In addition, the yield of the isolated adducts improved from 59% to 100%.

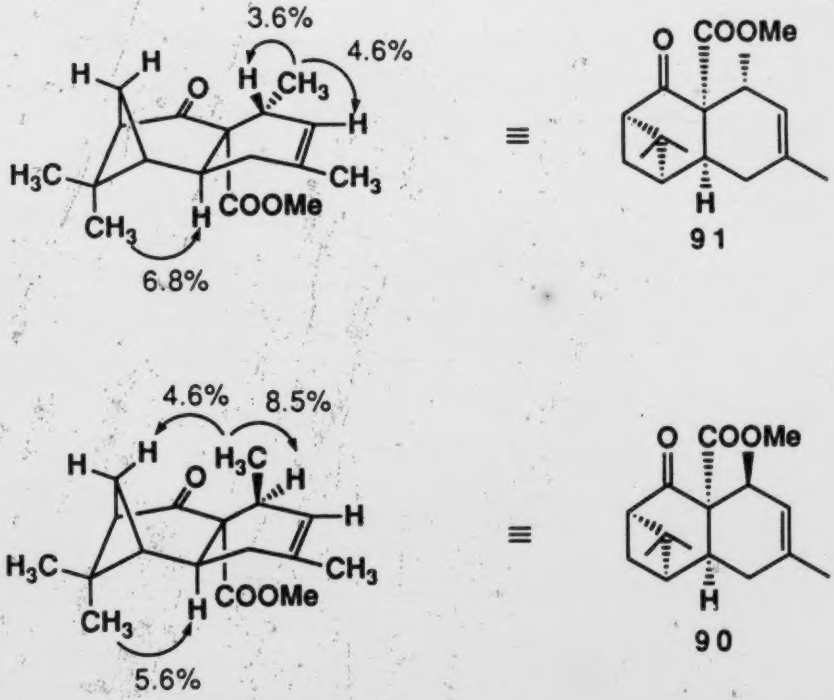


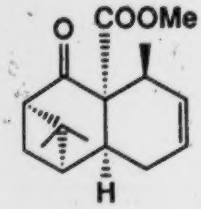
**Figure 1**. NOE data for adducts **90** and **91**

### C. Addition to *trans*-piperylene

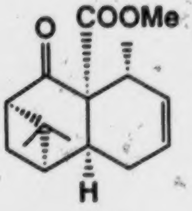
When an ethereal solution of enone ester **27** was reacted with *trans*-piperylene at -20°C using zinc chloride catalysis, two adducts, in a ratio of 86 : 14 (72% diastereomeric excess) were obtained in 77% yield. These adducts were separated by flash chromatography on silica gel. The fast eluting minor isomer displayed a specific rotation of $[\alpha]_D^{23}$ +153° (c. 1.66, $CHCl_3$) and its mass spectrum showed a molecular ion peak at m/z 262.1569 which was in agreement with the formula $C_{16}H_{22}O_3$. The IR spectrum exhibited strong absorptions at 1724 and 1710 $cm^{-1}$ indicating the presence of an ester and a ketone function respectively. The $^1H$ NMR spectrum displayed two vinylic protons at δ 5.97 (dddd) and 5.80 (dddd), and a methoxy singlet at δ 3.77. Two methyls appeared as singlets at δ 1.33 and 0.90 (*gem*) along with a methyl doublet at δ 1.06. In the $^{13}C$ NMR APT spectrum, two carbonyl carbons appeared at δ 209.76 and 173.96 while the carbons of the double bond resonated at δ 133.07 and 127.01.

The slower eluting major isomer showed a specific rotation of $[\alpha]_D^{23}$ +44.9° (c. 1.50, $CHCl_3$) and its IR spectrum showed carbonyl absorptions at 1744, 1721 (ester) and 1709 (ketone) $cm^{-1}$. A molecular ion peak at m/z 262.1568 was observed in the mass spectrum which was in agreement with the formula $C_{16}H_{22}O_3$. This was supported by elemental analysis. Two vinylic protons at δ 5.92 (ddd) and 5.56 (ddd) and a methoxy singlet at δ 3.72

appeared in the $^1$H NMR spectrum. It also showed *gem*-dimethyl singlets at δ 1.34 and 0.94 and a methyl doublet at δ 1.30. The presence of a double bond was confirmed by signals at δ 132.49 and 126.90 in the $^{13}$C NMR APT spectrum, which also showed carbonyl signals at δ 208.36 and 171.89.



**92**



**93**

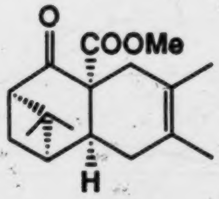
On the basis that the Diels-Alder reaction obeyed the normal *ortho*-rule, then the structures of the adducts were tentatively assigned as **92** and **93**. Previous observations indicated that the multiplicity and coupling pattern of the ring junction proton, $H_8$, could be used to determine the regiochemistry of the Diels-Alder adducts of 1-substituted dienes. Detailed $^1$H decoupling experiments of the major isomer showed that irradiation of the dddd at δ 2.90 ($H_8$, $J = 7.5, 7.5, 1.5, 1.5$ Hz), led to a change of multiplicity of the signals at δ 2.46 ($H_{11exo}$, $H_{7e}$), 2.11 ($H_9$) and 1.92 ($H_{7ax}$). When the signal at δ 2.11 ($H_9$) was irradiated, the signal at δ 2.90 ($H_8$) changed from a dddd to a ddd. Also, irradiation of the signal at δ 1.92 ($H_{7ax}$) resulted in a change of the multiplicity of the signal at δ 2.90 ($H_8$). Similarly, the $^1$H NMR spectrum of the minor isomer also showed a dddd at δ 3.25 ($H_8$, $J = 6.5, 6.5, 1.5, 1.5$ Hz). Like the previous case, this coupling pattern indicated that two hydrogens were attached to $C_7$ and consequently the methyl substituent had to be at $C_4$. Clearly, this data further confirmed the regiochemistry of the Diels-Alder adducts as shown by structures **92** and **93**.

To determine the stereochemistry of the ring junction and the $C_4$ methyl, NOE experiments were carried out. When the *endo* methyl (δ 0.94) of the major isomer was irradiated, a 5.7% NOE enhancement on $H_8$ (δ 2.90) was observed. Similarly, irradiation of the *endo* methyl (δ 0.90) of the minor isomer resulted in an NOE enhancement of 5.3% on $H_8$ (δ 3.25). This indicated that the $H_8$ proton was on the same face as the *gem*-dimethyl groups and therefore addition of diene occurred at the *Si*-face of enone ester **27**. The carbomethoxy group was then assigned in accordance with the *cis* principle. When the signal at δ 1.06 ($C_4$-$CH_3$) of the minor isomer was irradiated, 8.7% and 4% NOE enhancements on $H_4$ (δ 3.22) and $H_{11endo}$ (δ 1.86) respectively were observed. On the other hand, saturation of the signal at δ 1.30 ($C_4$-$CH_3$) of the major isomer resulted in 4.7% NOE enhancements on each of $H_4$ (δ 2.46) and $H_5$ (δ 5.56). This evidence unambiguously fixed the position and the stereochemistry of the substituents as that specified by the structure **92** for the minor isomer and **93** for the major isomer.

When two equivalents of zinc chloride were used in the Diels-Alder reaction of enone ester **27** and *trans*-piperylene, a single compound, adduct **93**, was obtained in 58% yield. The reaction proceeded at a faster rate than using one equivalent of catalyst, but the yield was lower. However, 100% diastereomeric excess (de) was achieved.

## D. Addition to 2,3-dimethylbutadiene

Enone ester **27** reacted with 2,3-dimethylbutadiene using zinc chloride as a catalyst to give a 1 : 1 adduct, in 93% yield. It displayed a specific rotation of $[\alpha]_D^{23}$ +68.97° (c. 1.07, $CHCl_3$). The $^{13}C$ NMR APT spectrum showed that the adduct was a single compound. The mass spectrum showed a molecular ion peak at m/z 276.1725 ($C_{17}H_{24}O_3$) and the IR spectrum showed bands at 1727 $cm^{-1}$ due to a saturated ester and at 1710 $cm^{-1}$ due to a ketone. The $^1H$ NMR spectrum showed two broad singlets at $\delta$ 1.68 and 1.65 due to two vinylic methyls and one singlet each at $\delta$ 3.76 (methoxy), 1.34 and 0.96 (*gem*-dimethyl). The spectral data was consistent with the proposed structure **94**.



**94**

As in the preceding cases, the stereochemistry was determined on the basis of the *cis*-principle and by an NOE experiment. Irradiation of the *endo* methyl ($\delta$ 0.96) resulted in NOE enhancements of 8.7% on $H_8$ ($\delta$ 3.18) and 3.7% on the *exo* methyl. This data supported the assignment of the stereochemistry of **94** which was in agreement with similar findings in this series, i.e. the diene added exclusively to the *Si*-face of enone ester **27**.

### E. Addition to 3-methyl-1,3-pentadiene

The diene, 3-methyl-1,3-pentadiene, was obtained from the Aldrich Chemical Co. as a mixture of *trans* and *cis* isomers. The ratio of this mixture was determined by $^1$H NMR to be 7 : 3. Comparison of the $^1$H NMR spectrum of this mixture, *trans*-piperylene and *cis*-piperylene (Table 6) clearly showed that the major isomer was *trans*-3-methyl-1,3-pentadiene.

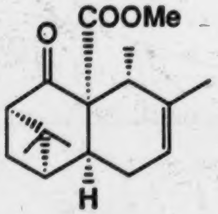
**Table 6.** $^1$H NMR data of 3-methyl-1,3-pentadiene, *trans*- and *cis*-piperylene

| Proton | 3-Methyl-1,3-pentadiene | | *trans*-Piperylene | *cis*-Piperylene |
|---|---|---|---|---|
| | major | minor | | |
| $H_{1a}$ | 4.92 | 5.09 | 4.93 | 5.08 |
| $H_{1b}$ | 5.08 | 5.20 | 5.07 | 5.17 |
| $H_2$ | 6.38 | 6.81 | 6.30 | 6.66 |
| $H_4$ | 5.58 | 5.47 | 5.71 | 5.52 |

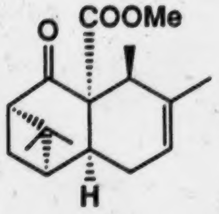
The zinc chloride catalysed addition of 3-methyl-1,3-pentadiene (mixture of *trans* : *cis* = 7 : 3) to enone ester **27** proceeded with a 76% consumption of enone ester **27** to give a 81 : 19 mixture of two isomeric adducts in 84% yield (based on the amount of starting material consumed). Separation by flash chromatography on silica gel produced two adducts in high purity.

The major (less polar) isomer displayed a specific rotation of $[\alpha]_D^{23}$ +99.65° (c. 2.56, $CHCl_3$) and a molecular ion peak at m/z 276.1726 ($C_{17}H_{24}O_3$) in its mass spectrum. The IR spectrum showed carbonyl bands at 1723 (ester) and 1702 (ketone) $cm^{-1}$. The $^1H$ NMR showed the presence of a vinylic proton as a multiplet at $\delta$ 5.60 and a vinylic methyl at $\delta$ 1.70 as a broad singlet. Other methyl groups appeared as singlets at $\delta$ 3.72 (methoxy), 1.33 and 0.93 (*gem*-dimethyl) and a doublet at $\delta$ 1.23. $^{13}C$ NMR APT spectrum confirmed the presence of a ketone ($\delta$ 208.74), an ester ($\delta$ 172.00) and a double bond ($\delta$ 138.76 and 122.10).

The minor (more polar) isomer showed a specific rotation of $[\alpha]_D^{23}$ +84.58° (c. 2.32, $CHCl_3$) and a molecular ion peak at m/z 276.1727 in the mass spectrum, corresponding to the formula $C_{17}H_{24}O_3$. The IR spectrum showed bands due to saturated ester at 1742 $cm^{-1}$ and a ketone at 1713 $cm^{-1}$. The $^1H$ NMR spectrum showed the presence of a vinylic proton at $\delta$ 5.64 as a broad doublet and a methoxy group as a singlet at $\delta$ 3.71. Methyl groups appeared as singlets at $\delta$ 1.34 and 0.82 (*gem*), as a doublet at $\delta$ 1.00, and as a doublet of doublets at $\delta$ 1.68 (vinylic)



**95**



**96**

If the Diels-Alder reaction followed the normal *ortho*-rule then the structures of the adducts could be tentatively assigned to be the keto esters **95** and **96**. The regiochemistry of both adducts was confirmed after close examination of the $^1$H NMR spectra and extensive $^1$H decoupling experiments on the minor isomer (Table 7). The signal at $\delta$ 3.28 due to the $H_8$ of the minor isomer, which showed a multiplicity of dddd ($J$ = 11, 7, 2, 2 Hz), was coupled to $H_{7ax}$ (11Hz), $H_{7e}$ (7 Hz), $H_9$ (2 Hz) and $H_{11exo}$ (W-coupling, 2 Hz). Similarly, the $H_8$ ($\delta$ 3.06) of the major isomer also showed a multiplicity of dddd with coupling constants of 8, 6, 1.5 and 1.5 Hz. In addition the $H_4$ at $\delta$ 3.04 of the minor adduct appeared as a quartet with a coupling constant of 7.5 Hz while the $H_4$ at $\delta$ 2.73 of the major adduct showed a multiplicity of broad quartet with a coupling constant of 7 Hz. In each case, this data indicates the presence of two protons on $C_7$ which requires that the methyl substituent be placed at $C_4$ and consequently the vinylic methyl substituent must be at $C_5$.

Evidence of the ring junction and the $C_4$ stereochemistry of both adducts was obtained from NOE experiments. Irradiation of the *endo* methyl ($\delta$ 0.93) of the major adduct resulted in an NOE enhancement of 5.9% on $H_8$ and saturation of the $C_4$-$CH_3$ ($\delta$ 1.23) led to a 6% NOE enhancement on $H_4$. When the *endo* methyl ($\delta$ 0.82) of the minor isomer was irradiated, a 4% NOE enhancement was observed on $H_8$, and when the $C_4$-$CH_3$ was saturated, 8.4% and 3.8% enhancements on $H_4$ and $H_{11endo}$ respectively were observed. On the basis of the *cis*-principle and these NOE

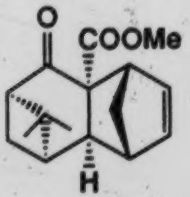
**Table 7**. $^1$H NMR data for adducts **95** and **96**

| 95<br>δ | 95<br>(multiplicity; *J* in Hz) | Proton | 96<br>δ | 96<br>(multiplicity; *J* in Hz) |
|---|---|---|---|---|
| 2.64 | (dd; 5.5, 5.5) | $H_1$ | 2.65 | (dd; 5.5, 5.5) |
| 2.73 | (br q; 7) | $H_4$ | 3.04 | (q; 7.5) |
| 5.60 | (m) | $H_6$ | 5.64 | (br d; 7.5) |
| 2.43 | (m) | $H_7$ | 2.18 | (ddd; 15, 7, 7) |
| 1.87 | (m) | $H_7$ | 1.88 | (m) |
| 3.06 | (dddd; 8, 6, 1.5, 1.5) | $H_8$ | 3.28 | (dddd; 11, 7.5, 2, 2) |
| 2.10 | (ddd; 6, 6, 2) | $H_9$ | 2.03 | (ddd; 6, 6, 2.5) |
| 2.43 | (m) | $H_{11}$*exo* | 2.51 | (dddd; 11, 6, 6, 2) |
| 1.97 | (d; 11) | $H_{11}$*endo* | 1.77 | (d; 11) |
| 1.23 | (d; 7) | $H_{12}$ | 1.00 | (d; 7.5) |
| 1.70 | (br s) | $H_{13}$ | 1.68 | (dd; 2.5, 1.5) |
| 1.33 | (s) | *exo* $CH_3$ | 1.34 | (s) |
| 0.93 | (s) | *endo* $CH_3$ | 0.82 | (s) |
| 3.72 | (s) | $OCH_3$ | 3.71 | (s) |

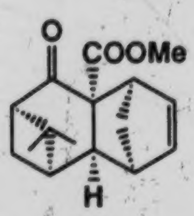
experiments, the stereochemistry of the major adduct and the minor adduct was established as that in **95** and **96** respectively. Again, this indicated that complete diastereofacial selectivity was achieved and the addition of diene was to the *Si*-face of enone ester **27**.

## F. Addition to cyclopentadiene

The zinc chloride catalyzed addition of cyclopentadiene to enone ester **27** produced a mixture of two inseparable adducts in the ratio of 89 : 11 (by $^1H$ NMR integration) in 53% yield. The IR spectrum of this mixture showed absorptions at 1731 and 1709 cm$^{-1}$, characteristic of the presence of an ester and a ketone respectively. The mass spectrum showed a molecular ion peak at m/z 260.1415, corresponding to the formula $C_{16}H_{20}O_3$. The $^1H$ NMR spectrum displayed two sets of signals in an integral ratio of 89 : 11. The major set showed two doublets of doublets at δ 6.46 and 5.98 indicative of the presence of two vinylic protons. Methyl singlets appeared at δ 3.67 (methoxy), 1.34 and 0.92 (*gem*). The minor set displayed two vinylic protons at δ 6.30 and 6.13 each as a doublet of doublets. Methyl singlets appeared at δ 3.76, 1.33 and 0.92 .



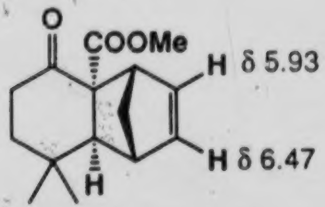
**97**



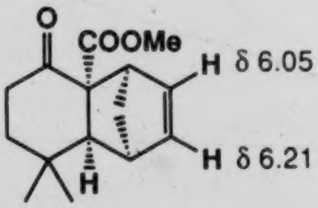
**98**

Preliminary analysis of the spectral data indicated that the structures of the adducts obtained could be assigned as **97** and **98**. Extensive $^1H$ decoupling experiments on the major isomer led to the assignment of all of its protons. The ring junction proton ($H_8$) appeared at δ 2.61 as a multiplet. Irradiation of the signals at δ 2.76 ($H_7$) and 2.42 ($H_9$) led to a small change in the multiplicity of the signal at δ 2.61. In an NOE experiment, when the *endo* methyl at δ 0.92 of the major isomer was irradiated, a 3% NOE enhancement on the signal at δ 2.61 was observed. On the basis of the *cis*-principle and this data, the major isomer was assigned with an α-$H_8$ and an α-carbomethoxy group.

Previous observations indicated that the addition of dienes to enone ester **27** occurred exclusively from the *Si*-face of **27**. It was therefore expected that exclusive addition of cyclopentadiene to the *Si*-face of **27** would occur. Consequently, the minor isomer would most likely contain an α-$H_8$ and an α-carbomethoxy group.



**99**

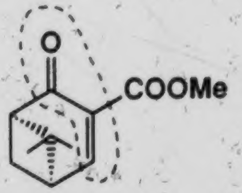


**100**

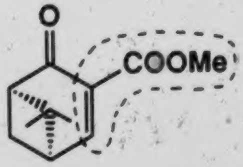
The stereochemistry of the methylene bridge on the bicyclo[2.2.1]heptene ring system was determined by comparing the difference in chemical shift between the two vinylic protons with the known compounds **99** and **100**.[122] Since the major isomer exhibited a larger difference in chemical shift between the two vinylic protons (Δδ 0.48) than the minor isomer (Δδ 0.17), it was accordingly assigned the structure **97** while the minor isomer was assigned structure **98**.

### G. Endo selectivities of the addition

The results in Table 2 show that the addition of dienes to enone ester **27** occurred with a diastereomeric excess of 62-100% and a discussion of this *endo*-selectivity is required. As illustrated by structures **27b** and **27c**, there are in fact two dienophilic components in enone ester **27**; these are the α,β-unsaturated ketone (**27b**) and the α,β-unsaturated ester (**27c**) moieties. Normally, it would be unnecessary to distinguish between these two moieties, except in certain cases where the *endo*-rule is in effect.

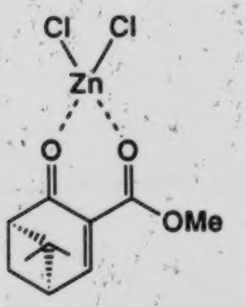


**27b**



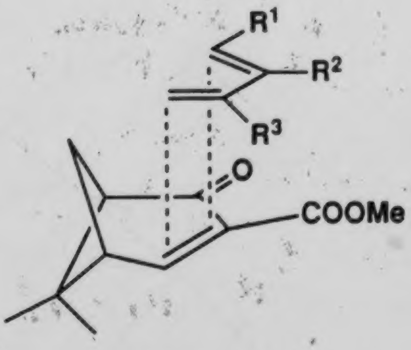
**27c**

*Endo*-addition to the enone or to the α,β-unsaturated ester moiety of **27** would give rise to stereochemically distinguishable products. The factor or factors determining which dienophilic moiety would dominate the reaction pathway is expected to be a function of the most effective secondary orbital overlap with the diene. It was observed that the addition of 1-substituted dienes (Table 2, Entries 1-4, 6, and 7) to enone ester **27** occurred predominantly by secondary overlap with the ester group (transition state **101**) rather than with the ketone carbonyl (transition state **102**). Comparison between the two transition states indicates that the addition *via* transition state **102** would encounter some steric interaction between the $C_2$-$C_3$ of the diene and the methylene bridge of the dienophile.

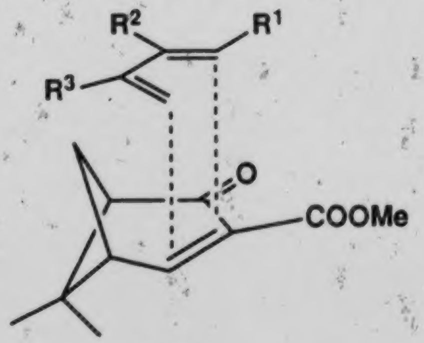


**27d**

The electronic influence exerted by zinc chloride on the Diels-Alder additions of enone ester **27** is most probably ascribed to the bidentate complexation of zinc chloride with the β-dicarbonyl (**27d**).



**101**



**102**

**101a** $R^1 = CH_3$, $R^2 = H$, $R^3 = CH_3$

**101b** $R^1 = CH_3$, $R^2 = H$, $R^3 = H$

**101c** $R^1 = CH_3$, $R^2 = CH_3$, $R^3 = H$

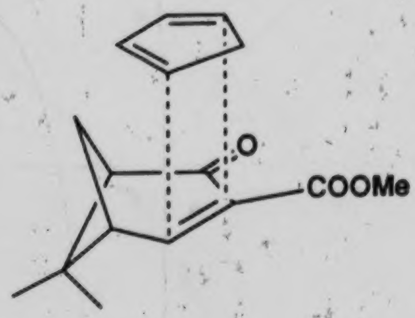
**102a** $R^1 = CH_3$, $R^2 = H$, $R^3 = CH_3$

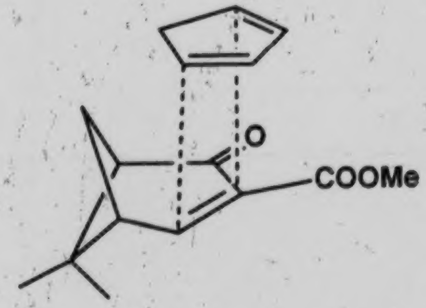
**102b** $R^1 = CH_3$, $R^2 = H$, $R^3 = H$

**102c** $R^1 = CH_3$, $R^2 = CH_3$, $R^3 = H$

The addition of *trans*-2-methyl-1,3-pentadiene to **27** at -20°C produced two $C_4$ epimeric adducts **90** and **91** in a ratio of 12 : 88. Keto ester **90** would be the result of addition *via* transition state **102a** while keto ester **91** would result from addition *via* transition state **101a**. The preferential formation of adduct **91** can be attributed at least in part to the destabilization of transition state **102a** by a steric interaction of the diene with the methylene bridge of the dienophile. On the other hand, addition *via* transition state **101a** would not encouter this steric interaction.

The cases of *trans*-piperylene (**92** and **93**) and cyclopentadiene (**97** and **98**) again showed good diastereoselectivity in favor of the adducts (**93** and **97**) resulting from addition of dienes *endo* to the ester group of **27** (transition state **101b** and **103**).





**103**

The addition of a mixture of *cis*- and *trans*-3-methyl-1,3-pentadiene (3 : 7) to **27** gave adducts **95** and **96** in a ratio of 81 : 19. **95** and **96** resulted from the addition of *trans*-diene to **27** *via* transition states **101c** and **102c** respectively. The ratio of these diastereomeric adducts **95** and **96** does not deviate from those of the other dienes utilized since the *trans*-diene is a much more reactive[69] diene than the *cis*-isomer and can compete effectively for the dienophile.

It was observed that the diastereoselectivity of the addition of *trans*-piperylene to **27** increased when two equivalents of zinc chloride were used. The reason for this result was not clear. However, in future it would be interesting to investigate the possibility that diastereoselectivity can be increased by the use of an excess of catalyst and a lower reaction temperature.

## H. Optical purity

As stated earlier, 92% optically pure (-)-β-pinene was used to prepare enone ester **27**. After we had demostrated the feasibility of the Diels-Alder reaction of enone ester **27**, the optical purity of the Diels-Alder adducts was analyzed. Optically active NMR shift reagents, such as $Eu(hfc)_3$ have been used to evaluate the optical yield of reactions.[123, 124] The direct application of $Eu(hfc)_3$ to adduct **85** showed a separation of the signals for the methoxy group (δ 3.75) and the vinylic methyl (δ 1.72). The $\Delta\delta$ increased with increasing amount of $Eu(hfc)_3$. The results obtained are summarized in Table 8. In all experiments, the integral of the split signals were consistently in the ratio of 96 : 4. This indicated that the optical purity (92%) was retained in the Diels-Alder adducts. Since both enantiomers of β-pinene are readily available, one can prepare enantiomeric sets of Diels-Alder adducts with high optical purity.

In conclusion, the Diels-Alder reactions of enone ester **27** with various dienes provided good to high yields of chiral adducts with complete diastereofacial selectivity in 62-100% diastereomeric excess. The observed regiochemistry was as predicted by the *ortho*- and *para*-rules. In this work we have shown that enone ester **27** is a new, versatile intermediate and in addition is also a useful chiral reagent for synthetic chemists.

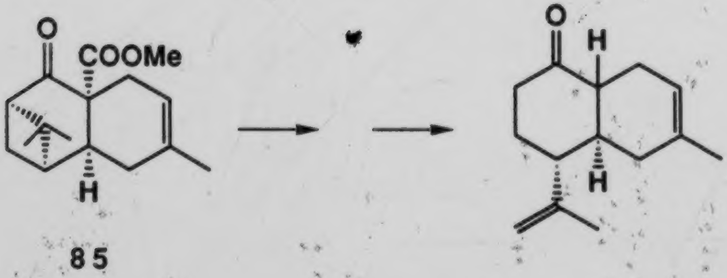
**Table 8**. Splitting of methyl signals in the $^1$H NMR spectrum (400 MHz) of adduct **85**

| Eu(hfc)$_3$ (eq) | OCH$_3$ ($\Delta\delta$) | C$_6$-CH$_3$ ($\Delta\delta$) |
|---|---|---|
| 0.1 | 0.06 | 0.05 |
| 0.2 | 0.10 | 0.08 |
| 0.3 | 0.12 | 0.10 |
| 0.5 | 0.14 | 0.12 |

## II. CYCLOBUTANE RING FRAGMENTATION REACTIONS

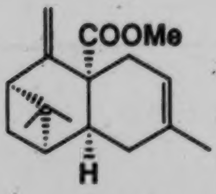
Having successfully generated various Diels-Alder adducts of enone ester **27**, we then wished to demonstrate the synthetic potential of **27** in the application to the synthesis of natural products. As shown in Scheme 9, the carbon skeleton of the cadinane sesquiterpenes can be readily obtained from adduct **85** after the cleavage of the cyclobutane ring system. The first requirement therefore was to cleave the cyclobutane ring system.

Scheme 9



85

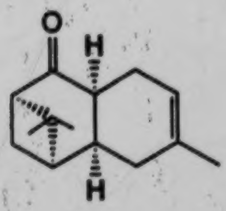
A number of methods have been previously reported for the fragmentation of the cyclobutane ring system of pinene derivatives.[96, 100, 125, 126] In 1989, Liu and Nyangulu[127] reported the fragmentation of pinenes to limonene derivatives using DMSO activated by phenyl dichlorophosphate. In order to apply this method, the transformation of **85** to **104** by a Wittig reaction was attempted without success. The desired product was not obtained, instead the starting material was recovered virtually unchanged. The failure of this reaction is most likely due to the fact that the ketone carbonyl is sterically hindered by the neighbouring groups. Hence, it was deemed necessary that the carbomethoxy group be removed prior to the Wittig reaction.



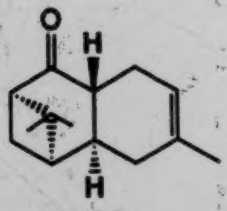
104

Treatment of **85** with lithium iodide monohydrate in 2,4,6-collidine under reflux condition for 2.3 h afforded two products in the ratio of 1 : 9 in 97% yield. After chromatographic separation, two pure compounds were obtained. The less polar minor isomer showed a specific rotation of $[\alpha]_D^{23}$ +107.3° (c. 2.07, $CHCl_3$) and a molecular ion peak at m/z 204.1512 in the mass spectrum indicating the formula $C_{14}H_{20}O$. The IR spectrum displayed a carbonyl absorption at 1705 $cm^{-1}$. The $^1H$ NMR spectrum showed a vinylic proton signal as a doublet of multiplets at δ 5.67 and a vinylic methyl as a broad singlet at δ 1.78. Methyl singlets also appeared at δ 1.34 and 0.91 (*gem*).

The more polar major isomer displayed a specific rotation of $[\alpha]_D^{23}$ -47.8° (c. 2.286, $CHCl_3$) and in the IR spectrum an absorption at 1714 $cm^{-1}$, characteristic of a ketone carbonyl was observed. The mass spectrum showed a molecular ion peak at m/z 204.1516 in agreement with the formula $C_{14}H_{20}O$. The $^1H$ NMR spectrum displayed a vinylic proton at δ 5.48 as a broad singlet, a vinylic methyl as a broad singlet at δ 1.70 and two singlets for the *gem*-dimethyl at δ 1.38 and 0.78. The presence of both ketone carbonyl (δ 214.74) and a double bond (δ 135.59 and 121.16) were confirmed by the $^{13}C$ NMR spectrum.



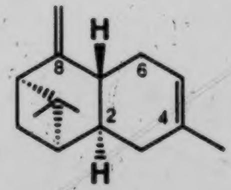
**105**



**106**

Based on this spectral data, structures **105** and **106** were assigned to the products. The stereochemistry of $C_3$ and which product was the major isomer remained to be determined. Extensive $^1H$ decoupling experiments of the minor isomer resulted in the assignment of all protons. The ring junction proton, $H_8$, appeared at δ 2.30 as a multiplet and its multiplicity changed when the following protons were irradiated individually: $H_{11exo}$ (δ 2.47), $H_9$ (δ 2.06) and $H_7$ (δ 1.99). Irradiation of the signals at δ 2.58 ($H_1$) and 1.82 ($H_{4ax}$) led to changes of the signal at δ 2.36 ($H_3$), indicating a long range W-coupling between $H_1$ and $H_3$. In an NOE experiment, irradiation of the *endo* methyl (δ 0.91) resulted in a 5.5% NOE enhancement on $H_3$ and $H_8$. This evidence indicated that the minor isomer could be assigned structure **105** while the major isomer could be assigned as structure **106**.

In order to confirm the stereochemistry of $C_3$, the minor isomer was epimerized with sodium hydroxide in aqueous methanol producing a mixture of **105** and **106** in a ratio of 1 : 9, respectively, in 92% yield.

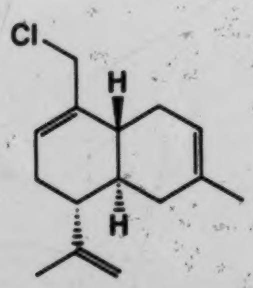


**107**

The transformation of ketone **106** to the desired product **107** was effected by a Wittig reaction using the procedure developed by Corey.[128] Treatment of **106** with methylenetriphenylphosphorane at room temperature for 20 h afforded **107** in 99% yield. A specific rotation of $[\alpha]_D^{23}$ -84.67° (c. 2.10, $CHCl_3$) was displayed by compound **107**. The mass spectrum showed a molecular ion peak at m/z 202.1722 corresponding to the formula $C_{15}H_{22}$.

The $^1$H NMR spectrum indicated the presence of three vinylic protons at $\delta$ 5.47, 4.66 and 4.60 and methyl singlets at $\delta$ 1.29 and 0.66 (*gem*). The $^{13}$C NMR spectrum showed a series of signals at $\delta$ 153.74, 135.65, 121.50 and 103.85 indicating the presence of two double bonds.

Compound **107** was then subjected to the fragmentation conditions developed by Liu and Nyangulu. Compound **107** was added to a mixture of DMSO and phenyl dichlorophosphate at -40°C. The mixture was stirred at this temperature for 1 h and allowed to warm up to 10°C over a period of 45 min.. After distillation, a 56% yield of a pale yellow solid with a melting point of 40-41°C was obtained. It was found that purification by distillation gave a larger amount of product than that obtained using flash chromatography (36%).



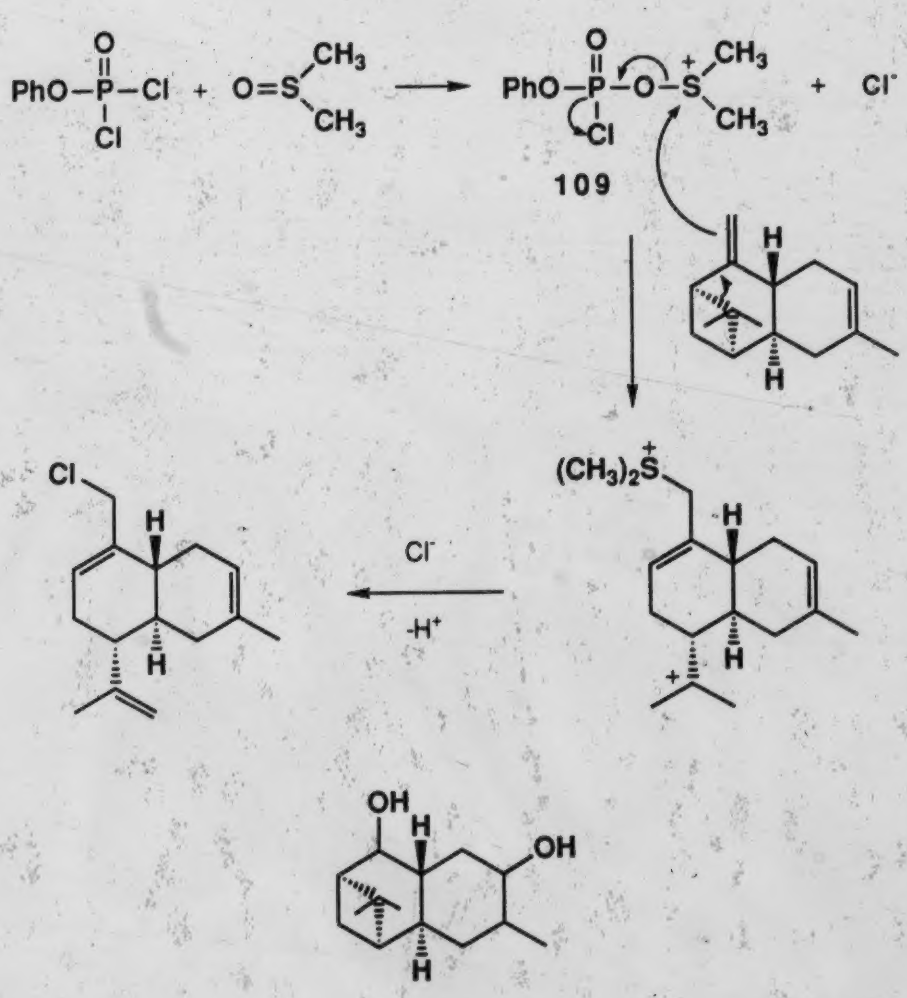
**108**

The product exhibited a specific rotation of $[\alpha]_D^{26}$ -193.9° (c. 2.33, $CHCl_3$) and two molecular ion peaks at m/z 238.1305 and 236.1331 in the mass spectrum, which were in agreement with the chemical formula $C_{15}H_{21}Cl$. The IR spectrum showed absorption at 1643 cm$^{-1}$ suggesting the presence of double bonds. The $^1$H NMR spectrum displayed four vinylic protons at δ 5.86, 5.49 and 4.78 (2H) and two vinylic methyls at δ 1.67. The geminal protons of the chloromethyl group appeared at δ 4.20 and 3.95. The $^{13}C$ NMR spectrum showed signals due to the three double bonds at δ 146.88, 136.36, 134.42, 127.85, 120.20 and 112.25. This spectral data suggested structure **108** for the product. The stereochemistry probably remained unchanged as no other epimeric isomer was isolated.

The formation of **108** can be rationalized as outlined in Scheme 10. Complex **109**,[129] which results from the interaction of dimethyl sulfoxide and phenyl dichlorophosphate, serves as an electrophile. Selective electrophilic attack on the exocyclic double bond induces the cleavage of the cyclobutane ring and the loss of a $H^+$ ion. The allylic sulfonium ion is then readily replaced by a chloride anion.

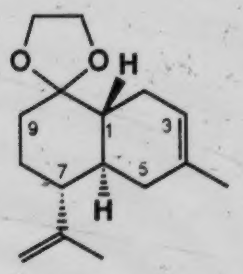
The facile rearrangement of **107** to **108** provided a useful route to the cadinane type of sesquiterpene. However, since **108** contains three double bonds it was anticipated that this might create problems in selectively functionalizing each of these double bonds. Consequently, the trisubstituted double bond of **106** was reacted with borane in THF, followed by the addition of hydrogen peroxide to give a mixture of two compounds in the ratio of 1 : 2 in quantitative yield. The IR spectrum of the mixture showed a hydroxyl absorption at 3362 $cm^{-1}$ and no carbonyl absorption band. The $^{1}H$ NMR spectrum showed two sets of two protons α to a hydroxyl group. The major set was at δ 4.21 and 3.65 and the minor one was at δ 3.92 and 3.31. Although the molecular ion peak corresponding to the molecular formula was not observed in the mass spectrum of the compound, fragments resulting from the loss of a $H_2O$ unit at m/z 206.1669 ($C_{14}H_{22}O$) and from the loss of two $H_2O$ units at m/z 188.1562 ($C_{14}H_{20}$) were observed. Using this information, structure **110** was assigned to the compounds.

**Scheme 10**

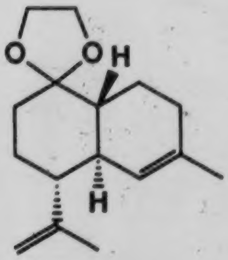


**110**

To prevent the undesired reduction of the ketone carbonyl, the ketone function must be protected prior to hydroboration. Treatment of **106** with *p*-toluenesulfonic acid and ethylene glycol in benzene under reflux conditions (water was removed by a Dean-Stark apparatus) for 20 h, gave surprisingly an inseparable mixture of two fragmentation products **111** and **112** in a 2 : 1 ratio in 81% yield. The mass spectrum of the mixture showed a molecular ion peak at m/z 248.1774, consistent with the formula $C_{16}H_{24}O_2$. No carbonyl absorption band was observed in the IR spectrum. The mixture showed a four-proton multiplet of the acetal moiety at δ 3.95 in the $^1H$ NMR spectrum. The major compound displayed vinylic protons at δ 5.27 (broad singlet, $H_3$) and 4.65 (2H) while those for the minor compound appeared at δ 5.15 (quartet, $H_5$), 4.81 and 4.65.



**111**

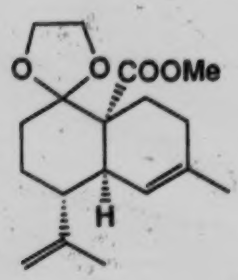


**112**

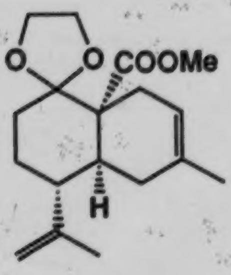
The stereochemistry of the ring junction was thought to be *trans* as the *trans* ring junction should have been thermodynamically more stable than the *cis*. Epimerization at $C_7$ was not expected as migration of the isopropenyl double bond was not observed. Since migration of the double bond during the acetalization reaction of an octalin system was not unprecedented,[130] the products were tentatively assigned the structures **111** and **112**.

It had been reported[72] that the $^1$H NMR data could differentiate between the *cis*-and *trans*-fused pairs of cadinenes with $\Delta^{4,5}$. In the *cis*-fused compounds there is a significant coupling between the olefinic proton and the bridgehead $H_6$, whereas in the *trans* isomers there is either little or no coupling between these two protons. Examination of molecular models indicated that **112** probably contains a β-orientated $H_1$, i.e. a *trans* ring junction. The coupling constant of 1.5 Hz for $H_5$ (q) is most likely due to the long range coupling with the vinylic methyl group since the dihedral angle between $H_6$ and $H_5$ is about 90°.

Having discovered this somewhat unexpected ring cleavage reaction, we then undertook an investigation of this reaction with various other substrates. Acetalization of **85** with *p*-toluenesulfonic acid and ethylene glycol in benzene under reflux conditions for 48 h afforded the inseparable ring cleavage products **113** and **114** in the ratio of 41 : 59 in 92% yield (based on consumed starting material); 54% of the starting material was recovered. The reaction was sluggish due to the fact that the ketone carbonyl is sterically hindered.



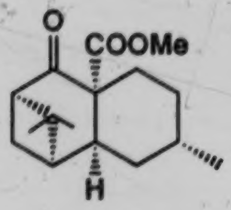
**113**



**114**

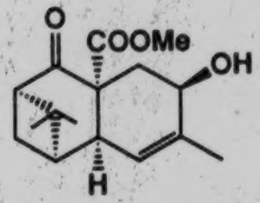
The mixture showed an absorption for the ester group at 1729 $cm^{-1}$ in the IR spectrum and a molecular ion peak at m/z 306.1830 in the mass spectrum, which was in accordance with the formula $C_{18}H_{26}O_4$. Multiplets at δ 4.75 and 3.79-4.00 in the $^1$H NMR spectrum were assigned to the vinylic protons of the isopropenyl group and the protons of the acetal moiety, respectively. In addition, **113** showed a doublet of quartets at δ 5.37 for $H_5$ ($J$ = 5, 1.5 Hz) while the $H_3$ of **114** appeared at δ 5.30 as a broad singlet. The difference of the multiplicities of the two vinylic protons suggested that the two products arose as a result of the migration of the double bond. This observation supported the previous assignment of compounds **111** and **112**.

In order to ascertain the product of the ring cleavage reaction, without the complication of the migration of the double bond, the trisubstituted double bond of **85** was hydrogenated using platinum oxide as the catalyst at 35 psi in ethanol and a trace amount of glacial acetic acid for 24 h. After flash chromatography, a quantitative yield of **115** was obtained.



**115**

Compound **115** displayed a specific rotation of $[\alpha]_D^{26}$ +122.62° (c. 1.7, $CHCl_3$) and its mass spectrum showed a molecular ion peak at m/z 264.1724 consistent with the formula $C_{16}H_{24}O_3$. The IR spectrum displayed strong absorption bands at 1737 and 1707 cm$^{-1}$, characteristic of an ester and a ketone carbonyl. The presence of the ester and ketone moieties was verified by the $^{13}C$ NMR APT spectrum which displayed signals at δ 210.33 and 172.56. Additional evidence was provided by the $^1H$ NMR spectrum which indicated that no vinylic proton was present. Methyl singlets were observed at δ 3.80 (methoxy), 1.37 and 1.01 (*gem*) together with a methyl doublet at δ 0.86.

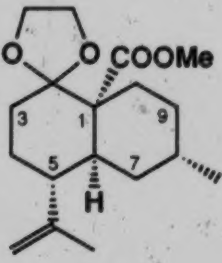


**116**

Extensive $^1H$ decoupling experiments enabled all protons to be correctly assigned. Most of the signals for the protons in the cyclohexane ring were close together, for example $H_5$, $H_6$ and $H_7$, which affected the results of the NOE experiments. Examination of a molecular model of **85** showed that the addition of hydrogen probably occurred from the less hindered face, opposite to the carbomethoxy group. In this case, **115** would then have an α-$CH_3$ on $C_6$. Photooxygenation of **85** (which will be discussed in a later section), also supported this assignment. In this reaction, the oxygen adds exclusively to the less hindered face to give a single product after reduction,

**116**. On the basis of this observation, the stereochemistry of $C_6$ was tentatively assigned as in structure **115**.

Using the same ring cleavage reaction conditions, **115** was treated with *p*-toluenesulfonic acid and ethylene glycol for 100 h. After purification, a single compound **117** was obtained in 64% yield (based on the amount of consumed starting material) and 70% of the starting material was recovered. Compound **117** showed an infrared absorption at 1728 $cm^{-1}$ corresponding to an ester group. A molecular ion peak was observed at m/z 308.1992 which was in agreement with the molecular formula $C_{18}H_{28}O_4$. The $^1H$ NMR spectrum displayed two signals for vinylic protons at $\delta$ 4.76 and 4.73. The methoxy singlet appeared at $\delta$ 3.73 and the $C_8$ methyl signal occurred at $\delta$ 0.75 as a doublet.

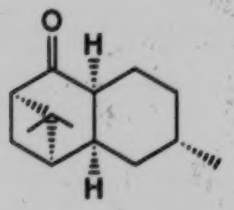


**117**

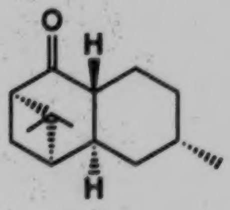
The ring cleavage reaction of **115** proceeded very slowly with only 30% conversion of starting material. This was due to the fact that the ketone carbonyl was sterically hindered by the carbomethoxy group and so it had to be removed. Treatment of **115** with lithium iodide monohydrate in refluxing 2,4,6-collidine provided two compounds in quantitative yield after purification by column chromatography on silica gel.

The fast eluting minor isomer showed a specific rotation of $[\alpha]_D^{26}$ +96.13° (c. 0.766, $CHCl_3$) and had a mp of 32-33°C. Its mass spectrum showed a molecular ion peak at m/z 206.1665 consistent with the formula $C_{14}H_{22}O$. A carbonyl band was observed at 1707 $cm^{-1}$ in the IR spectrum, which was confirmed by the appearance of a signal at $\delta$ 216.68 in the $^{13}C$ NMR APT spectrum. The $^1H$ NMR displayed methyl singlets at $\delta$ 1.34 and 0.90 (*gem*) and a methyl doublet at $\delta$ 0.98.

The more slowly eluting major isomer displayed a specific rotation of $[\alpha]_D^{26}$ +66.71 (c. 1.67, $CHCl_3$) and its IR spectrum showed only one carbonyl absorption at 1712 $cm^{-1}$ (ketone). The $^{13}C$ NMR APT spectrum supported the presence of a ketone by a signal at $\delta$ 214.94. Methyl singlets at $\delta$ 1.36 and 0.80 in the $^1H$ NMR spectrum were attributed to the *gem*-dimethyl groups. A methyl doublet at $\delta$ 1.05 was also observed. The mass spectrum showed a molecular ion peak at m/z 206.1666, corresponding to the formula $C_{14}H_{22}O$.



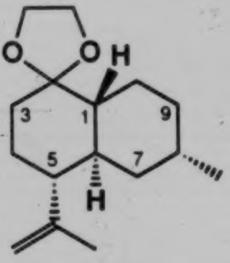
**118**



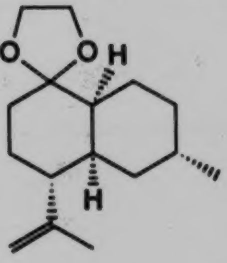
**119**

From the spectral data, the two decarbomethoxylated compounds were assigned structures **118** and **119**. The stereochemistry of $C_3$ remained to be determined. The minor isomer was epimerized with sodium hydroxide in aqueous methanol to give an equilibrium mixture of the minor and major isomers in a ratio of 3 : 7, respectively, in 97% yield. Subsequently, structures **118** and **119** could be assigned to the minor and major isomer, respectively.

Ketone **119** was then subjected to the same ring cleavage reaction. Reaction of **119** with *p*-toluenesulfonic acid and ethylene glycol in refluxing benzene with removal of $H_2O$ by a Dean-Stark trap for 48 h gave acetals **120** and **121** in 92% yield in a ratio of 54 : 46 respectively. Two pure acetals were obtained after separation by chromatography on silica gel.



**120**

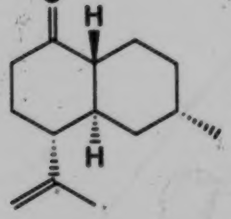


**121**

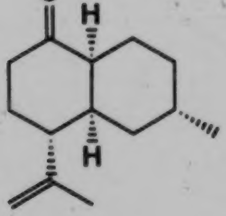
The less polar major compound **120** displayed a specific rotation of $[\alpha]_D^{26}$ -13.9° (c. 1.50, $CHCl_3$) and had an observed mp of 39-41°C. Its IR spectrum showed a weak absorption for the carbon-carbon double bond at 1646 $cm^{-1}$. The mass spectrum displayed a molecular ion peak at 250.1931 corresponding to the formula $C_{16}H_{26}O_2$. In the $^1H$ NMR spectrum, the broad singlet at $\delta$ 4.69 was assigned to the two vinylic protons. The four protons of the acetal moiety appeared as a multiplet at δ 3.93 and the $C_8$-methyl appeared as a doublet at δ 0.96.

The more polar minor isomer **121** showed a specific rotation of $[\alpha]_D^{26}$ +27.7° (c. 1.15, $CHCl_3$) and melted between 60-61°C. Its IR spectrum showed a weak carbon-carbon bond absorption at 1644 $cm^{-1}$ and a molecular ion peak at 250.1930, corresponding to the formula $C_{16}H_{26}O_2$, was observed in the mass spectrum. The $^1H$ NMR spectrum showed two vinylic protons as a broad singlet at δ 4.73 and an acetal unit at δ 3.94. A methyl doublet was also observed at δ 0.80.

This spectral data supported the assignment of the structures **120** and **121** to the isomer. In order to determine the stereochemistry of $C_1$, both acetals were subjected to transacetalization reactions. Treatment of **120** with *p*-toluenesulfonic acid in refluxing aqueous acetone for 3 h gave ketone **122** in quantitative yield. Ketone **122** displayed a specific rotation of $[\alpha]_D^{26}$ -11.12° (c. 0.80, $CHCl_3$) and melted between 71-73°C. The IR spectrum showed the presence of a ketone carbonyl band at 1712 $cm^{-1}$. The presence of a ketone function was also confirmed by a signal at δ 212.30 in the $^{13}C$ NMR APT spectrum, which also showed the presence of a double bond by signals at δ 146.58 and 112.26. The mass spectrum displayed a molecular ion peak at m/z 206.1674 consistent with the formula $C_{14}H_{22}O$. Signals attributed to two vinylic protons were observed at δ 4.78 as a multiplet in the $^1H$ NMR spectrum.

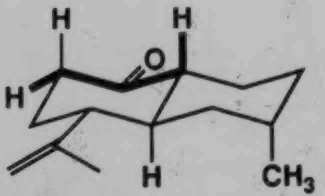


**122**

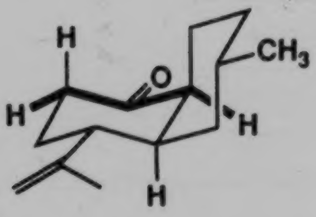


**123**

When acetal **121** was treated with *p*-toluenesulfonic acid in refluxing aqueous acetone for 3.5 h, ketone **123** was obtained in 85% yield. Ketone **123** showed a specific rotation of $[\alpha]_D^{26}$ +106.75° (c. 1.17, $CHCl_3$) and its mass spectrum showed a molecular ion peak at m/z 206.1659 in agreement with the molecular formula $C_{14}H_{22}O$. In the IR spectrum, a ketone carbonyl absorption was observed at 1710 $cm^{-1}$. The $^{13}C$ NMR APT spectrum further confirmed the presence of a ketone group by a signal at δ 215.15. A signal corresponding to two vinylic protons appeared at δ 4.72 in the $^1H$ NMR spectrum.



**122a**



**123a**

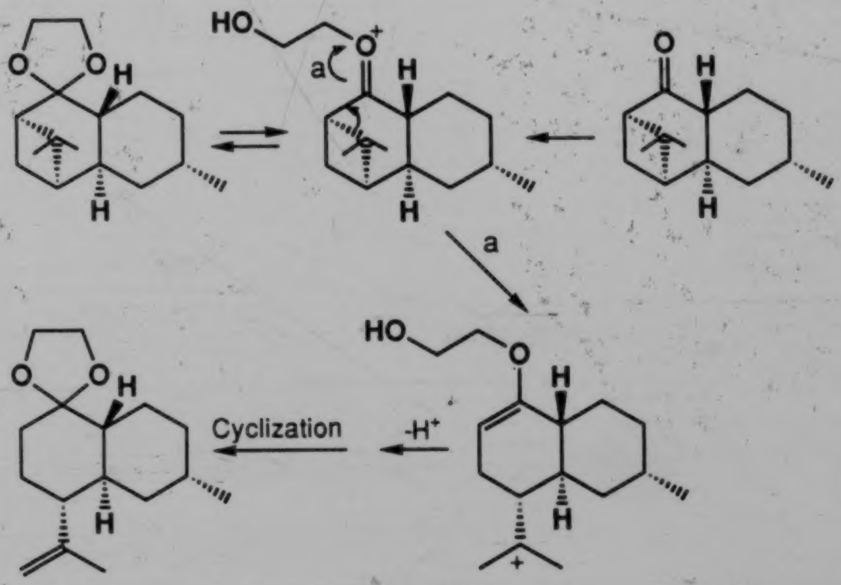
Since distinctive resonances were displayed by some single protons in the $^1H$ NMR spectrum, the spectrum of **123** was informative with regards to the stereochemistry of $C_1$. Extensive $^1H$ decoupling experiments led to the assignment of the cyclohexanone protons. By irradiating the signal at δ 2.40, $H_1$ (dddd, $J$ = 12, 4.5, 4, 1 Hz), it was determined that this proton had a W-coupling of 1 Hz to the signal at δ 2.28 , $H_{3e}$ (dddd, $J$ = 15, 4, 2, 1 Hz). An examination of a molecular model revealed that ketone **123** would have the conformation **123a** in which a long range W-coupling between $H_1$ and $H_{3e}$ would be expected to be observed in the $^1H$ NMR spectrum. On the other hand, in **122a** such a W-coupling would not be expected.

In order to fully determine the stereochemistry of $C_1$, ketone **123** was epimerized with sodium hydroxide in aqueous methanol to give an equilibrium mixture of **122** and **123** in a ratio of 74 : 26 respectively, in 73% yield. Consequently, the $C_1$ of acetal **120** was assigned with a β-orientated $H_1$ and the $H_1$ of **121** was assigned as being α-orientated.

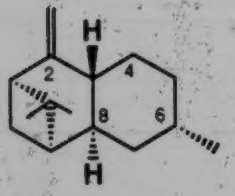
This newly developed fragmentation reaction, employing *p*-toluenesulfonic acid and ethylene glycol was found to be clean and gave high yields of product. One important feature of this ring cleavage reaction is that under this mild reaction condition, no epimerization of the $C_5$ stereogenic center was observed.

We were interested in evaluating a possible mechanism for this reaction. To this end an investigation was carried out to determine if fragmentation occurred without ethylene glycol being present. Treatment of **119** with *p*-toluenesulfonic acid in refluxing benzene for 41 h, resulted in the formation of a complex mixture. Six spots, including the starting material, were observed by TLC. This indicated that ethylene glycol was essential for fragmentation to occur cleanly. Based on this fact a plausible mechanism for the fragmentation reaction is shown (Scheme 11).

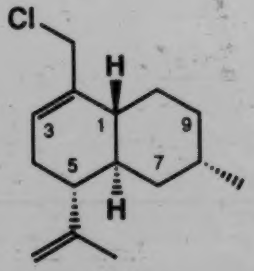
**Scheme 11**



Since the fragmentation reaction of **107** with phenyl dichlorophosphate and DMSO gave only a moderate yield of the fragmentation product **108**, this fragmentation reaction was also carried out on **124** (which was prepared from ketone **119**) to see that if the yield could be improved. Thus the Wittig reaction of ketone **119** with methylenetriphenylphosphorane at room temperature for 20 h gave **124** in 90% yield. Compound **124** displayed a specific rotation of $[\alpha]_D^{26}$ +28.83° (c. 0.822, $CHCl_3$) and a weak double bond absorption at 1640 $cm^{-1}$ in the IR spectrum. In the mass spectrum, the molecular ion was observed at m/z 204.1888, which was in agreement with the formula $C_{15}H_{24}$. Additional evidence for the exocyclic double bond was obtained from the $^1$H NMR spectrum, which showed signals for two vinylic protons at δ 4.67 and 4.55, each appearing as a doublet of doublets. The $^{13}$C NMR spectrum confirmed the presence of the double bond by signals at δ 154.07 and 103.03.



**124**



**125**

Compound **124** was then treated with phenyl dichlorophosphate and DMSO at -45 to -50 °C for 24 h. After all the starting material had been consumed, aqueous sodium bicarbonate was added to remove excess phenyl dichlorophosphate or other phosphorus compounds. After purification, compound **125** was obtained in 61% yield. It displayed a specific rotation of $[\alpha]_D^{26}$ -34.21° (c. 0.95, $CHCl_3$) and a mp between 73-75°C. The IR spectrum showed absorptions at 1644 and 1658 $cm^{-1}$ characteristic of carbon-carbon double bonds. Three vinylic protons appeared as multiplets at δ 5.81 and 4.73 (2H) in the $^1$H NMR spectrum. The mass spectrum showed molecular ion peaks at m/z 240.1465 and 238.1490, in agreement with the molecular formular $C_{15}H_{23}Cl$.

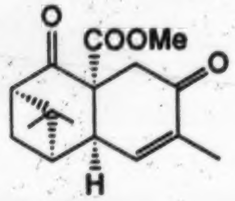
Since **107** and **124** gave almost the same yield of fragmentation products, it seems likely that the trisubstituted double bond in **107** does not affect the yield of the reaction.

## III. TOTAL SYNTHESIS OF SESQUITERPENES: (+)-METHYL LEDESMATE AND (-)-METHYL ZAFRONATE

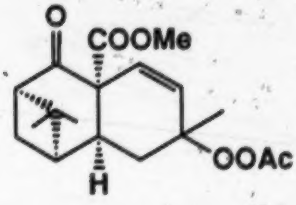
The Diels-Alder adduct **85**, was envisioned as a good precusor for the synthesis of sesquiterpenes for several reasons. Firstly, as demonstrated earlier, the fragmentation of the cyclobutane ring system would provide the bicyclo[4.4.0]decanone ring system with retention of two stereogenic centers ($C_5$ and $C_6$). These stereogenic centers would provide a handle to determine or to confirm the relative stereochemistry of the natural products. Secondly, the $C_2$ ketone could be used to control the $C_1$ stereogenic center after decarbomethoxylation, and this ketone could then be readily converted to a tertiary alcohol. Finally, the trisubstituted double bond was suitably functionalized to be transformed into the allylic alcohol in the final products.

Adduct **85** was not a suitable substrate for the ring cleavage reaction by *p*-toluenesulfonic and ethylene glycol since the ketone carbonyl was sterically hindered and double bond migration occurred during the reaction. Hence, we decided to convert the trisubstituted double bond into an α,β-unsaturated ketone. This conversion would provide the correct regiochemistry of the double bond in the final products and could later be used to differentiate between this double bond and the isopropenyl group.

One way of effecting this transformation was by photooxygenation.[131] The photooxygenation reaction was preferable because it involved a single step conversion. A solution of **85**, acetic anhydride, pyridine, tetraphenylporphine and dimethylaminopyridine in dichloromethane was bubbled with a gentle stream of oxygen and irradiated with two 200W tungsten lamps for 13 h. After flash chromatography and recrystallization from dichloromethane-petroleum ether, compound **126** was obtained in 90% yield. Compound **126**, obtained as colorless hexagonal crystals, displayed a specific rotation of $[\alpha]_D^{25}$ +137.10° (c. 1.55, $CHCl_3$) and a mp of 109-110°C. The IR spectrum showed absorptions at 1735 $cm^{-1}$ for the ester carbonyl; 1711 $cm^{-1}$ for the ketone carbonyl and 1678 $cm^{-1}$ for the carbonyl of the enone system. The $^1H$ NMR showed a signal at $\delta$ 6.47 (dq, $J$ = 5, 1 Hz) for the $\beta$-enone proton. The signals at $\delta$ 3.32 (d, $J$ = 18 Hz) and 2.67 (d, $J$ = 18 Hz) were assigned to the two $\alpha'$-protons of the enone carbonyl. The mass spectrum showed a molecular ion peak at m/z 276.1355, which was in agreement with the expected molecular formula $C_{16}H_{20}O_4$. The presence of an enone was also confirmed by the $^{13}C$ NMR spectrum which displayed signals at $\delta$ 194.03 (enone carbonyl), 135.83 and 144.25 ($\alpha$- and $\beta$-vinylic carbons of the enone).



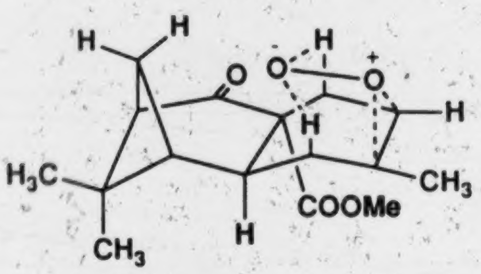
**126**



**127**

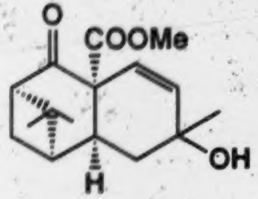
During flash chromatography, a small amount (1%) of compound **127** was also isolated. The mass spectrum of this compound showed a molecular ion peak at m/z 336.1575, corresponding to the molecular formula $C_{18}H_{24}O_6$. In the IR spectrum, the ester and ketone functions showed strong absorptions at 1731 and 1712 $cm^{-1}$ respectively. The vinylic protons resonated at $\delta$ 5.95 and 4.53, each signal appeared as a doublet ($J$ = 8 Hz) in the $^1H$ NMR spectrum. Methyl singlets appeared at $\delta$ 1.71, 1.34 and 1.04. In the $^{13}C$ NMR APT spectrum, three carbonyl signals were observed at $\delta$ 209.68, 172.28 and 169.54. The signals for the two olefinic carbons appeared at $\delta$ 139.48 and 105.55, and the carbon bearing the peracetoxy group resonated at $\delta$ 105.95.

We were surprised and somewhat delighted to obtain compound **126**, with the endocyclic double bond, as the only product. None of the compound with the exocyclic double bond, enone system was isolated. Over the years a large number of mechanisms have been proposed for photooxygenation reactions.[132-134] The formation of **126** could be explained by the involvement of the interaction of the type suggested in structure **128**. Abstraction of $H_7$ would lead to the formation of compound **126** while abstraction of $H_4$ would lead to the formation of compound **127**. Since $H_4$ was $\beta$ to a ketone and an ester carbonyl, abstraction of this more acidic proton was expected to be favorable. On the other hand, abstraction of $H_7$ would form a more stable trisubstituted double bond. Experimentally, abstraction of $H_7$ occurred almost exclusively and the reason for this was not clear.

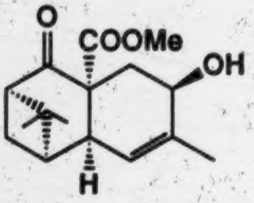


**128**

In theory, $^1O_2$ can attack the double bond from either or both of the $C_5$-*Si* and $C_5$-*Re* faces. We were interested to find out if there was any diastereofacial selectivity (like the hydrogenation reaction) in this reaction. It was possible to determine this diastereofacial selectivity by preparing the allylic alcohol instead of the enone. Thus, keto ester **85** in dichloromethane containing a catalytic amount of tetraphenylporphine was bubbled with oxygen and irradiated with two 200W tungsten lamps for 3 h. The hydroperoxide obtained was then reduced by triphenylphosphine at 0°C to give a virtually quantitative yield of the secondary allylic alcohol **116** as well as trace amounts of the tertiary allylic alcohol **129**.



**129**



**116**

The IR spectrum of compound **129** showed a broad hydroxyl absorption at 3480 cm$^{-1}$ and carbonyl bands at 1731 and 1711 cm$^{-1}$ corresponding to the presence of an ester and a ketone respectively. Two vinylic protons, each as a doublet of doublets, were observed at δ 5.92 and 5.82 in the $^1$H NMR spectrum. The $^1$H NMR also showed four methyl singlets at δ 3.79, 1.37, 1.31 and 1.05. Although in the high resolution mass spectrum, the molecular ion corresponding to the expected molecular formula was not observed, a fragment resulting from the loss of a methanol unit was observed at m/z 246.1253 ($C_{15}H_{18}O_3$). Its molecular weight which was in accord with the expected formula $C_{16}H_{22}O_4$, was verified by chemical ionization mass spectrometry to be 278.

Compound **116**, which was almost the only product formed, showed a specific rotation of $[\alpha]_D^{22}$ +58.57° (c. 0.84, $CHCl_3$). Attempted recrystallization of **116** failed to give any crystalline compound. The IR spectrum showed absorptions at 3280 cm$^{-1}$ for the hydroxyl group, 1724 cm$^{-1}$ for the ester carbonyl and 1705 cm$^{-1}$ for the ketone carbonyl. A molecular ion peak at m/z 278.1516, corresponding to the molecular formula $C_{16}H_{22}O_4$, was observed in the mass spectrum, which also showed the [$M^+$-$H_2O$] peak at m/z 260.1413 and [$M^+$-$CH_3OH$] peak at m/z 246.1255. The $^1$H NMR spectrum showed the presence of a vinylic proton at δ 5.24 as a multiplet and methyl singlets appeared at δ 3.81, 1.81, 1.39 and 0.99. Evidence of the stereochemistry of $C_5$ was obtained from $^1$H decoupling and NOE experiments. In the $^1$H decoupling experiments, irradiation of the signal at δ 4.11 ($H_5$) led to the simplification of the signals at δ 5.24 ($H_7$, m→dd), 2.82 ($H_{4e}$, dd→d), 1.81 ($H_{4ax}$) and 1.70 (OH, d→s). The protons on the cyclohexanone ring were similar in chemical shift and coupling pattern to the enone **126**. In the NOE experiments, saturation of the signal at $\delta$ 3.44 ($H_8$) resulted in an NOE enhancement of 8.4% for the signal at $\delta$ 2.11 ($H_9$), 9.2% for $\delta$ 0.99 (*endo* $CH_3$) and 11.4% for $\delta$ 5.24 ($H_7$). In addition, when the signal at $\delta$ 1.96 ($H_{11endo}$) was irradiated, an NOE enhancement of 30% for $H_{11exo}$, 6.8% for $H_{4ax}$, -3.8% for $H_{4e}$ and -3.2% for the *exo* methyl were observed. These experiments suggested that the allylic alcohol **116** had the conformation depicted in figure 2.

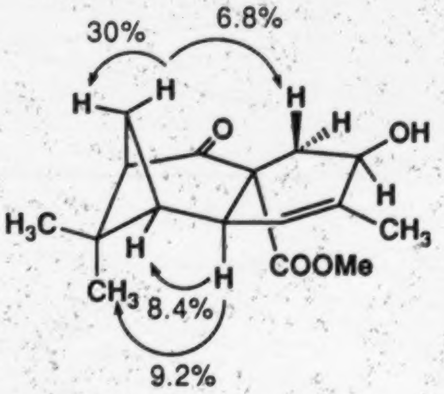
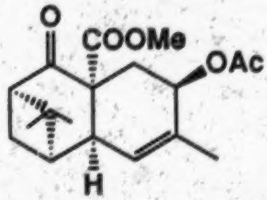


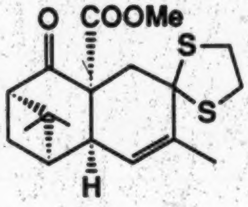
**Figure 2**. NOE data of compound **116**

From the examination of a molecular model, if $H_5$ was equatorial, then two small coupling constants would be observed each on $H_{4ax}$ and $H_{4e}$. On the other hand, if $H_5$ was axial, a large *trans*-diaxial coupling constant would be expected on $H_{4ax}$ and a smaller value for the coupling constant on $H_{4e}$. Since the multiplicity and hence the coupling constant of $H_{4ax}$ was obscured by the signal for the vinylic methyl, the alcohol was acetylated in the hope that the signal of $H_{4ax}$ could be resolved. Consequently, alcohol **116** was treated with acetic anhydride and pyridine at room temperature to give a quantitative yield of acetate **130**. A specific rotation of $[\alpha]_D^{22}$ +41.93° (c. 1.5, $CHCl_3$) was observed for **130**. In the IR spectrum, carbonyl bands were observed at 1741 (ester) and 1711 $cm^{-1}$ (ketone). Its mass spectrum showed a molecular ion peak at m/z 320.1625 consistent with the formula $C_{18}H_{24}O_5$. In the $^1H$ NMR spectrum, a singlet due to the acetate group appeared at $\delta$ 2.08. It was observed that the $H_5$ signal had shifted downfield to $\delta$ 5.35 from $\delta$ 4.11 observed for **116**. The signal at $\delta$ 2.83 ($H_{4e}$) appeared as a doublet of doublets with a geminal coupling constant of 13 Hz and a smaller coupling constant of 5.5 Hz with $H_5$. Also, $H_{4ax}$ had shifted downfield from $\delta$ 1.80 (for that of **116**) to $\delta$ 1.86 and appeared as a doublet of doublets with a geminal coupling of 13 Hz and a *trans*-diaxial coupling constant of 10.5 Hz. Evidently, the hydroxyl group in **116** was β-orientated. Consequently, the addition of $^1O_2$ appears to occur exclusively from the $C_5$-*Re* face.



**130**

With enone ester **126** in hand, the next step involved the selective protection of the enone carbonyl as a thioacetal. It was thought that the sterically hindered ketone carbonyl would not undergo thioacetalization. A thioacetal functionality was chosen due to its high thermal stability and stability towards acids, bases and chromatographic purification. Its high tolerance to a wide range of reaction conditions would allow the thioacetal funtionality to be carried through multistep operations. Initial attempts to selectively protect the enone carbonyl by treatment of **126** with 1,2-ethanedithiol and boron trifluoride etherate at room temperature did not produce the desired product, although at 0°C a small amount of impure thioacetal was isolated. In both reactions, the saturated ketone carbonyl also reacted since no ketone carbonyl absorption was observed in the IR spectrum of the by-products. Subsequently, the reaction was repeated with lower temperatures such as -20°C and -30°C. Eventually, -10°C was selected as the best temperature for this reaction. Treatment of **126** with 1,2-ethanedithiol in the presence of boron trifluoride etherate in dichloromethane at -10°C for 76 h provided the thioacetal **131** in 98% yield (based on 64% of the starting material consumed).



**131**

Thioacetal **131** displayed a specific rotation of $[\alpha]_D^{28}$ -60.2° (c. 0.804, $CHCl_3$) and a mp between 143-145°C (dichloromethane-petroleum ether). The IR spectrum showed an absorption of the ketone carbonyl at 1712 $cm^{-1}$ and the disappearance of the enone carbonyl band. A molecular ion peak in the mass spectrum at m/z 352.1170 was consistent with the formula $C_{18}H_{24}O_3S_2$. The $^1H$ NMR spectrum showed a signal for the vinylic proton at $\delta$ 5.41 as a doublet of quartets and a methoxy singlet at $\delta$ 3.82. The protons of the thioacetal unit appeared as multiplets at $\delta$ 3.44 (1H), 3.31 (2H) and 3.15 (1H). The *gem* dimethyls appeared at $\delta$ 1.36 and 0.86 each as a singlet indicating that the cyclobutane ring was intact. In the $^{13}C$ NMR APT spectrum, the ketone carbonyl resonated at $\delta$ 206.69 and the ester carbonyl was observed at $\delta$ 170.67. The vinylic carbons appeared at $\delta$ 135.01 and 129.03.

It was vital that the ring junction proton ($\alpha$-$H_8$) of the product with the correct stereochemistry, did not epimerize during the reaction. A NOE study on thioacetal **131** was performed which provided evidence for the retention of stereochemistry of $H_8$. By saturating of the signal at $\delta$ 0.86 (*endo* methyl), an enhancement of 7% was observed at $\delta$ 3.75 ($H_8$). When the complementary experiment was carried out, i.e. when the signal at $\delta$ 3.75 ($H_8$) was irradiated, an enhancement of 10% was observed at $\delta$ 0.86 (*endo* methyl). This indicated that $H_8$ and the *endo* methyl were in close proximity and this consequently established the $\alpha$-orientation of $H_8$.

It seemed that from this initial work thioacetal **131** could be readily prepared in high yield. However, when the reaction was scaled up from 300 mg to 1 g under the same reaction conditions used previously, only 19% of the starting material was consumed after 88 h. The effect of various mole ratios of

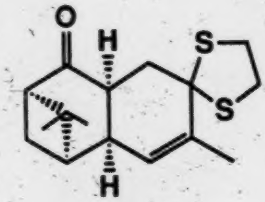
**Table 9**. Thioacetalization of compound **126** under various conditions

| Entry | **126** (mmol) | $BF_3 \cdot OEt_2$ (eq) | $(SHCH_2)_2$ (eq) | Time (h) | % **126** consumed | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | 0.20 | 0.4 | 1.00 | 38 | 100 | 93 |
| 2 | 1.12 | 0.4 | 1.06 | 76 | 64 | 98 |
| 3 | 0.36 | 1.1 | 1.10 | 37 | 93 | 85 |
| 4 | 0.31 | 0.4 | 2.00 | 36 | 100 | 81 |
| 5 | 3.70 | 0.4 | 1.06 | 88 | 19 | 96 |
| 6 | 0.37 | 1.0 | 2.00 | 33 | 100 | 71 |
| 7 | 3.00 | 1.0 | 1.05 | 70 | 64 | 100 |
| 8 | 1.06 | 0.6 | 1.00 | 71 | 90 | 88 |
| 9 | 1.85 | 1.0 | 1.03 | 71 | 84 | 91 |
| 10 | 4.00 | 1.8 | 1.07 | 66 | 76 | 91 |

boron trifluoride etherate and 1,2-ethanedithiol in the reaction was investigated. The results are summarized in Table 9. The amount of 1,2-ethanedithiol required relative to **131** was found to be 1 : 1, as excess 1,2-ethanedithiol lowered the yield of product (Entries 4 and 6). As the amount of starting material increases, it is essential to use more than one equivalent of boron trifluoride etherate relative to **131** in order to achieve high conversion.

Inherent in this sequence of reactions was the necessity of removing the carbomethoxy group. Decarbomethoxylation was achieved by treatment of

**131** with lithium iodide monohydrate in 2,4,6-collidine under reflux conditions for 3 h. After chromatographic purification, a single compound was isolated in 91% yield. This compound displayed a specific rotation of $[\alpha]_D^{25}$ -145.49° (c. 0.91, $CHCl_3$) and a mp of 161-162°C after recrystallization from ether-petroleum ether. In the IR spectrum, a single absorption at 1696 $cm^{-1}$ corresponding to the carbonyl of the ketone was observed. In the mass spectrum, the molecular ion was observed at m/z 294.1122, which was in agreement with the formula $C_{16}H_{22}OS_2$. The $^1H$ NMR showed the disappearance of the methoxy singlet and the presence of *gem* dimethyl singlets at $\delta$ 1.36 and 0.91 indicating that the cyclobutane ring was intact. The presence of a signal for the vinylic proton was also observed as a doublet of quartets at $\delta$ 5.33 together with the thioacetal moiety at $\delta$ 3.20-3.46. The spectral data was in accordance with the assignment of gross structure **132** to the decarbomethoxylated product.



**132**

To assign all the protons of compound **132**, a number of $^1H$ decoupling experiments were carried out. By irradiation of the signal at $\delta$ 3.03 ($H_3$), it was determined that this proton was coupled to the signals at $\delta$ 2.74 ($H_8$), 2.61 ($H_{4e}$) and 2.13 ($H_{4ax}$). Similarly, by irradiation of the signal at $\delta$ 2.74 ($H_8$), it was determined that this proton was coupled to $H_7$ ($\delta$ 5.33), $H_3$

($\delta$ 3.03), $H_{11exo}$ ($\delta$ 2.40), $H_9$ ($\delta$ 2.13) and the protons of the vinylic $CH_3$ ($\delta$ 2.01). After the assignment of the protons was complete, NOE experiments were carried out to determine the stereochemistry of $C_3$. Saturation of the signal at $\delta$ 3.03 ($H_3$), resulted in an enhancement of 4.6% on *endo* $CH_3$, 6.8% on $H_{4e}$ and 13.7% on $H_8$. When the signal at $\delta$ 0.91 (*endo* $CH_3$) was irradiated, enhancements of 4% on the *exo* $CH_3$, 5.5% on $H_8$, and 4.2% on $H_3$ were observed. Evidently, the ring junction protons $H_3$, $H_8$ and the *endo* $CH_3$ were in close proximity to each other. This established the *cis* relationship between $H_3$ and $H_8$ and the fact that both were α-orientated as depicted in figure 3.

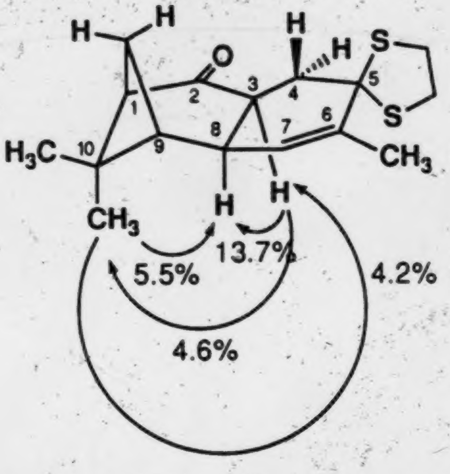
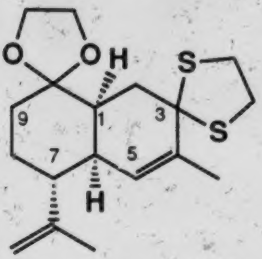


**Figure 3**. NOE data of compound **132**

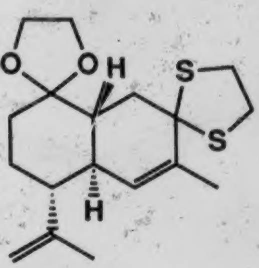
With the structure of ketone **132** firmly established, the next step of the synthesis involved the fragmentation of the cyclobutane ring system using the method developed as described in section II. Accordingly, compound **132** was treated with *p*-toluenesulfonic acid and ethylene glycol in refluxing benzene with removal of water for 24 h. The reaction was monitored by TLC. It was found that the product had the same $R_f$ as the starting material if ethyl acetate-petroleum ether was used as the developing solvent. However, they could be differentiated by multiple development with 3% methanol in petroleum ether. The crude product was purified by flash chromatography on silica gel to give two isomeric products in the ratio 85 : 15 in 98% yield.

The less polar major isomer displayed a specific rotation of $[\alpha]_D^{24}$ -97.5° (c. 0.8, $CHCl_3$) and a mp of 134-135°C. The $^1H$ NMR spectrum showed signals for three vinylic protons at $\delta$ 5.48 and 4.75 (2H). The protons of the acetal unit appeared at $\delta$ 3.91-4.08 and those of the thioacetal moiety appeared at $\delta$ 3.21-3.48. The $^{13}C$ NMR APT spectrum displayed signals for four vinylic carbons at $\delta$ 147.18, 135.02, 130.10 and 111.45, and in addition signals for the carbon bearing the two oxygens at $\delta$ 109.78 and the carbon bearing the two sulfur atoms at $\delta$ 70.14 were observed. The mass spectrum showed a molecular ion peak at 338.1372 consistent with the formula $C_{18}H_{26}O_2S_2$.

The more polar minor isomer showed a specific rotation of $[\alpha]_D^{24}$ +31° (c. 1.50, $CHCl_3$) and a molecular ion peak at m/z 338.1375 in agreement with the formula $C_{18}H_{26}O_2S_2$. The $^1H$ NMR spectrum displayed three vinylic protons at $\delta$ 5.39 (multiplet), 4.83 (multiplet) and 4.76 (a broad singlet). It also showed the protons of the acetal unit at $\delta$ 3.92-4.05 and the thioacetal unit at $\delta$ 3.21-3.47. The presence of four vinylic carbons was confirmed by signals at $\delta$ 147.27, 135.56, 128.91 and 112.36 in the $^{13}C$ NMR APT spectrum, which also confirmed the presence of the carbon bearing the two oxygens at δ 109.19 and the carbon bearing the two sulfur atoms at δ 70.10. Based on the spectral data, structures **133** and **134** could be assigned to the products.

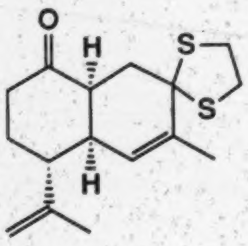


**133**

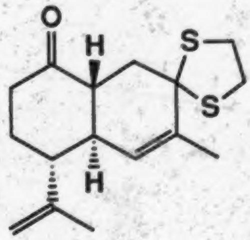


**134**

The stereochemistry of $C_1$ and the assignment of the major and minor products remained to be determined. Transacetalization of the major compound with acetone in the presence of *p*-toluenesulfonic acid gave ketone **135** in quantitative yield. Ketone **135** was obtained in the form of needle-shaped crystals after recrystallization from dichloromethane-petroleum ether, the crystal melted between 146-147°C. Compound **135** displayed a specific rotation of $[\alpha]_D^{23}$ -77.78° (c. 0.765, $CHCl_3$) and a molecular ion peak at m/z 294.1112 consistent with the formula $C_{16}H_{22}OS_2$ in the mass spectrum. The IR spectrum showed a carbonyl absorption at 1708 $cm^{-1}$. The $^1H$ NMR spectrum showed the disappearance of the acetal unit and vinylic proton signals appeared at δ 5.47, 4.86 and 4.82. The presence of a carbonyl was confirmed by a signal at δ 212.78 in the $^{13}C$ NMR APT spectrum.



**135**

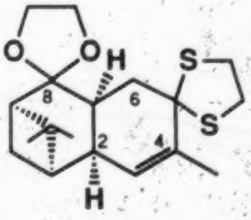


**79**

Similarly, the minor compound was also transacetalized with acetone in the presence of *p*-toluenesulfonic acid to give ketone **79** in 84% yield. Ketone **79** displayed a specific rotation of $[\alpha]_D^{23}$ +81.08° (c. 1.09, $CHCl_3$) and melted at 139-140°C after being recrystallized from dichloromethane-petroleum ether. Absence of the protons of the acetal moiety in the $^1H$ NMR spectrum and the observation of a ketone carbonyl band at 1716 $cm^{-1}$ in the IR spectrum indicated the transacetalization had in fact taken place. A molecular ion peak at m/z 294.1120 corresponding to the formula $C_{16}H_{22}OS_2$ was observed in the mass spectrum. The $^{13}C$ NMR APT spectrum confirmed the presence of a ketone carbonyl by a signal at $\delta$ 210.40.

In order to determine the stereochemistry of $C_1$, ketone **135** was epimerized with sodium hydroxide in aqueous methanol to give ketone **79** in 97% yield. This established that **133** was the major acetal and **134** was the minor acetal.

For large scale preparation, the three steps (fragmentation, transacetalization and epimerization) were carried out without purification of the intermediates. Ketones **135** and **79** were obtained with an overall yield of 88% in the ratio of 9 : 91 respectively. These two compounds were separated by flash chromatography on silica gel.



**136**

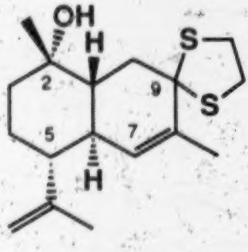
When monitoring the fragmentation reaction by TLC, in addition to the spots for the starting material and products, another spot was observed in the early stage of the reaction which disappeared when the reaction was complete. We were curious as to the identity of this species as it was thought that it could be the intermediate acetal proposed in the mechanism (Scheme 11). Hence ketone **132** was treated with *p*-toluenesulfonic acid (0.1 eq) and ethylene glycol in refluxing benzene for 3 h. Acetals **136** and **133** were obtained along with 72% recovery of the starting material. The presence of the vinylic proton at δ 5.21 ($H_7$) and the *gem*-dimethyl at δ 1.23 (*exo* $CH_3$) and 1.01 (*endo* $CH_3$) in the $^1H$ NMR spectrum of **136** indicated that the cyclobutane ring was intact. The $^1H$ NMR spectrum also showed the acetal unit at δ 3.90 as a multiplet. The mass spectrum showed a molecular ion peak at m/z 338.1373, corresponding to the formula $C_{18}H_{26}O_2S_2$. The $^{13}C$ NMR APT spectrum confirmed the presence of an acetal by a signal at δ 113.58.

The *cis* ring junction of acetal **136** was determined based on the following observation. Deacetalization of **136** with *p*-toluenesulfonic acid in refluxing moist benzene gave ketone **132**.

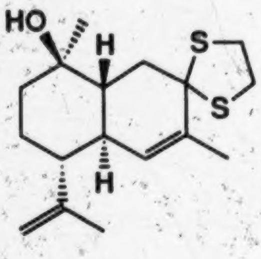
When acetal **136** in benzene (dried) was treated with *p*-toluenesulfonic acid (in the absence of ethylene glycol) under reflux conditions with removal of water by a Dean-Stark apparatus for 1 h, a mixture of acetals **133** and **134** in the ratio of 4 : 1 was obtained. Using the same reaction conditions, ketone **132** gave no fragmentation product and only starting material was recovered. This sequence of reactions provided the evidence that the fragmentation reaction occurred *via* the formation of acetal **136** as proposed in Scheme 11.

With ketone **79** in hand, the next step of the synthesis involved the addition of methyllithium to **79**. Reaction of **79** with methyllithium in ether at 0°C for 3 h produced two epimeric tertiary alcohols. After separation by flash chromatography on silica gel, two pure alcohols were obtained in the ratio of 2.7 : 1 in 78% yield. The fast eluting major compound gave white crystals that melted at 113-114°C after recrystallization from ether-petroleum ether and displayed a specific rotation of $[\alpha]_D^{26}$ +11.86° (c. 1.94, $CHCl_3$). The IR spectrum showed an absorption at 3440 $cm^{-1}$ for the hydroxyl group. The $^1H$ NMR spectrum displayed singlets at $\delta$ 1.10 (OH, $D_2O$ exchangable) and at 1.27 (tertiary $CH_3$). The mass spectrum showed a molecular ion peak at m/z 310.1422 corresponding to the molecular formula $C_{17}H_{26}OS_2$ and a fragment at m/z 292.1316 due to the loss of a $H_2O$ molecule.

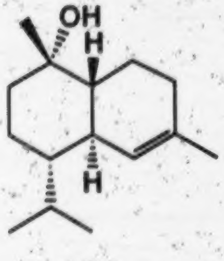
The slow eluting minor isomer, after recrystallization from dichloromethane-petroleum ether, displayed a mp of 65-66°C and a specific rotation of $[\alpha]_D^{23}$ -31.52° (c. 0.66, $CHCl_3$). In the IR spectrum, a hydroxyl absorption appeared at 3416 $cm^{-1}$. The $^1H$ NMR spectrum displayed singlets at $\delta$ 1.36 ($D_2O$ exchangable) and 1.16 (tertiary $CH_3$). A molecular ion peak at m/z 310.1424 consistent with the molecular formula $C_{17}H_{26}OS_2$ and a fragment due to the lost of a $H_2O$ molecule at m/z 292.1316 were observed in the mass spectrum.



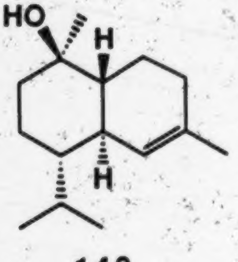
**137**



**138**



**139**



**140**

Based on the spectral data, structures **137** and **138** were assigned to the products. Comparison of the $^1H$ NMR spectrum of the two alcohols showed that the chemical shift of the protons were almost identical except for the tertiary hydroxyl and methyl group. The chemical shift of the $C_2$-$CH_3$ ($\delta$ 1.16) of the minor alcohol was at a slightly higher field (0.11 ppm) than that of the $C_2$-$CH_3$ ($\delta$ 1.27) of the major alcohol. Comparing this data with the known compounds (+)-T-cadinol (**139**) ($C_2$-$CH_3$ at $\delta$ 1.15) and (-)-α-cadinol (**140**) ($C_2$-$CH_3$ at $\delta$ 1.05)[72] suggested that the hydroxyl group of the minor alcohol was β-orientated (**138**) while that of the major alcohol was α-orientated (**137**). This assignment of the stereochemistry of $C_2$ was later proven by X-ray crystallography of "(-)-methyl zafronate".

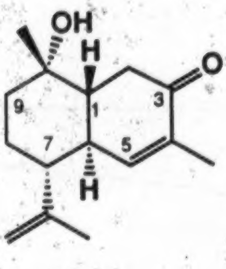
Both alcohols could be used in the synthesis of sesquiterpenes. Alcohol **138** had the correct stereochemistry at $C_2$ for the synthesis of (-)-methyl zafronate (**34**). On the other hand, alcohol **137**, which was obtained in good yield from the addition reaction, could be converted to the natural product (+)-methyl ledesmate (**38**) after elimination of the hydroxyl group.

**Table 10**. Various addition reactions of compound **79**

| Reagent | Solvent | Temp (°C) | Time | Yield (%) | Ratio (137 : 138) |
|---|---|---|---|---|---|
| $CH_3Li$ | ether | 0 | 3 h | 78 | 2.7 : 1 |
| $CH_3Li$ | ether | -78 | 3 h | 87 | 9.0 : 1 |
| $CH_3MgBr$ | THF | 0 | 40 min | 83 | 19 : 1 |
| $CH_3Li$, $CeCl_3$ | THF | 0 | 4.5 h | 90 | 1.3 : 1 |
| $CH_3Li$, $SmCl_3$ | THF | 0 | 43 h | - | 1.4 : 1 |

Before we proceeded with the synthesis of the natural products, an investigation of the addition reaction was undertaken. To improve the formation of alcohol **138**, various reaction conditions were tried (Table 10). At lower temperature (-78°C) the selectivity towards the alcohol **137** increased. A high stereoselectivity for **137** was also observed when the Grignard reagent, methylmagnesium bromide in THF was used. When cerium(III) chloride or samarium(III) chloride (vacuum dried) was introduced to a solution of ketone **79** in THF before the addition of methyllithium, the ratio of the alcohols was about 1 : 1. All these methods involving introduction of a methyl to the ketone carbonyl did not result in preferential formation of **138** as the addition invariably occurred from the *Re*-face of the carbonyl. In theory, introduction of a methylene group followed by oxidation would give the β-orientated hydroxyl group. However, this method was not applicable to ketone **79** which already has two double bonds in the molecule.

Having prepared alcohols **137** and **138**, we were ready to proceed with the synthesis of the natural products. Alcohol **137** which could be readily obtained, was used as the model compound for the required functional group transformations and finally converted to (+)-methyl ledesmate. At this stage, it was necessary to remove the thioacetal protecting group so that the two double bonds could be differentiated for the allylic oxidation. Dethioacetalization could be effected by utilizing salts of the transition-metal silver, titanium, copper, cadmium and mercury. Of these mercury(II) salts such as the perchlorate, chloride and oxide, have been the most widely used. Treatment of **137** with mercury(II) chloride and calcium carbonate in 80% aqueous acetonitrile[135] at room temperature for 2 h afforded enone **141** in 29% yield only. This compound appeared as white crystals (mp 131°C) after recrystallization from dichloromethane-petroleum ether, and displayed a specific rotation of $[\alpha]_D^{23}$ -25.14° (c. 1.24, $CHCl_3$). The IR spectrum showed a hydroxyl absorption at 3448 $cm^{-1}$ and a carbonyl band at 1661 $cm^{-1}$ for the conjugated ketone. The presence of the enone function was confirmed by signals at δ 200.44 (enone carbonyl), 148.35 and 134.90 (vinylic carbons) in the $^{13}C$ NMR APT spectrum. The mass spectrum showed a molecular ion peak at m/z 234.1620 in accordance with the expected molecular formula $C_{15}H_{22}O_2$. Further proof for the assigned structure **141** came from the $^1H$ NMR spectrum. A multiplet at δ 6.63 was attributed to the vinylic proton of the enone. The doublet of doublets at δ 2.63 and 2.41, each with a geminal coupling of 16.5 Hz, was assigned to the methylene protons adjacent to the enone carbonyl.

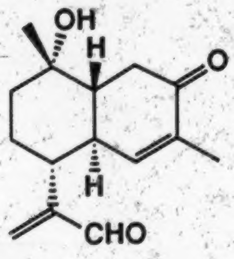


**141**

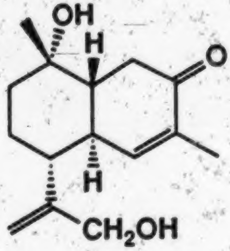
Since the mercury(II) chloride deacetalization reaction gave a poor yield of **141**, another transition metal salt, silver(I) oxide[136] was used. When **137** was treated with silver(I) oxide in aqueous methanol under reflux conditions for 19 h, a 71% yield of **141** was obtained. Attempts to obtain optically pure **141** by recrystallization from dichloromethane-petroleum ether showed no improvement in optical activity between the first and second recrystallization for this compound.

After the thioacetal of **137** had been successfully removed to form the enone **141**, the next step called for allylic oxidation of the isopropenyl side chain. One way of introducing the allylic alcohol or an aldehyde group was the photooxygenation reaction with which we already had some success. Consequently, **141** was irradiated (tungsten lamp) in the presence of acetic anhydride, pyridine, 4-dimethylaminopyridine and tetraphenylporphine with a slow stream of oxygen in dichloromethane for 42 h. However, no reaction occurred and only starting material was recovered. When this reaction was repeated with carbon tetrachloride as the solvent, none of the desired product was detected and as before only starting material was recovered. From these results it appeared that this terminal double bond was not reactive towards photooxygenation.

Another method commonly used for the allylic oxidation of olefins is to use selenium dioxide.[137, 138] Treatment of **141** with selenium dioxide (2-4 eq) in glacial acetic acid at various temperatures gave only 37-44% yields of the α,β-unsaturated aldehyde **142**. The improved procedure developed by Sharpless[139] was then tried whereby a catalytic or stoichiometric amount of selenium dioxide with *tert*-butyl hydroperoxide was employed. It was claimed that this method would eliminate color, organoselenium by-products and elemental selenium from the reaction products. The reaction of **141** with selenium dioxide (0.8 eq) and *tert*-butyl hydroperoxide (4 eq) in dichloromethane in the presence of a trace amount of acetic acid for 98 h at room temperature gave both the α,β-unsaturated aldehyde **142** (28% yield) and the allylic alcohol **143** (42% yield).



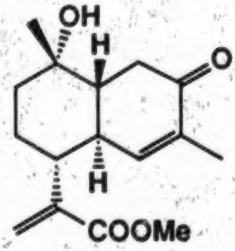
**142**



**143**

Compound **142** was produced as a white crystalline compound with a mp of 145-146°C after two recrystallizations from dichloromethane-petroleum ether. It displayed a specific rotation of $[\alpha]_D^{23}$ -66.3° (c. 1.11, $CHCl_3$). Its IR spectrum showed a strong hydroxyl absorption at 3460 $cm^{-1}$ and absorptions due to the conjugated carbonyl systems at 1687 and 1671 $cm^{-1}$. In the $^1H$ NMR spectrum, the aldehydic proton appeared at δ 9.62 as a singlet. The two vinylic protons of the α,β-unsaturated aldehyde group were observed at δ 6.42 and 6.23, each as a singlet. The hydroxyl proton at δ1.45 which appeared as a broad singlet was confirmed by its disappearance in a $D_2O$ exchange experiment. The mass spectrum showed a molecular ion peak at m/z 248.1410, corresponding to the expected molecular formula $C_{15}H_{20}O_3$.

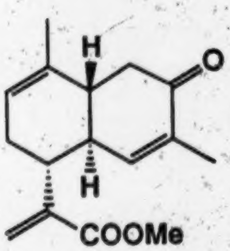
Compound **143** displayed a specific rotation of $[\alpha]_D^{23}$ -60.9° (c. 0.89, $CHCl_3$) and melted between 122-123°C after recrystallization from dichloromethane-petroleum ether. Its IR spectrum showed absorption due to the hydroxyl group at 3400 $cm^{-1}$ and a conjugated ketone carbonyl at 1659 $cm^{-1}$. A molecular ion peak m/z 250.1566 in agreement with the molecular formula $C_{15}H_{22}O_3$ was observed in the mass spectrum. In the $^1H$ NMR spectrum, signals for the three vinylic protons appeared at δ 6.66, 5.27 and 5.04 and the two α-protons of the hydroxyl group were observed as a broad doublet at δ 4.17.



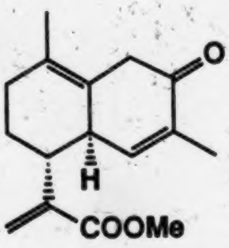
**144**

Conversion of the α,β-unsaturated aldehyde **142** and the allylic alcohol **143** to an α,β-unsaturated ester was effected in two steps. Treatment of **142** and **143** with Jones reagent [140] in acetone followed by methylation of the resulting acid in acetone with methyl iodide and anhydrous potassium carbonate gave compound **144** in 49% yield. This compound exhibited a specific rotation of $[\alpha]_D^{23}$ -72.13° (c. 2.72, $CHCl_3$) and a molecular ion peak at m/z 278.1516, consistent with the molecular formula $C_{16}H_{22}O_4$, in the mass spectrum. Its IR spectrum showed three distinct absorptions at 3493 (hydroxyl), 1718 (conjugated ester) and 1672 $cm^{-1}$ (conjugated ketone). The presence of an ester was also indicated by a singlet at δ 3.80 (methoxy) in the $^1H$ NMR spectrum. Signals for the three vinylic protons were also observed at δ 6.51, 6.04 and 5.70. The hydroxyl proton which appeared as a broad singlet at δ 1.16 was assigned based on a $D_2O$ exchange experiment.

At this stage, the synthetic scheme called for the elimination of the tertiary hydroxyl group. There are a number of procedures known to effect the dehydration of an alcohol to an alkene. It was thought that the tertiary alcohol could be easily dehydrated. However, treatment of **144** with phosphorus oxychloride or thionyl chloride and pyridine[141] gave a poor yield (13%) of the dehydrated product **145**. In both cases, no starting material was recovered. The absence of a hydroxyl absorption in the IR spectrum of **145** indicated that dehydration had taken place. Compound **145** showed signals at δ 6.64, 6.39, 5.65 and 5.44 for the vinylic protons in the $^1H$ NMR spectrum.



**145**



**146**

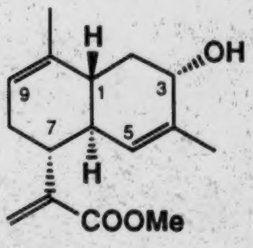
A combination of methanesulfonyl chloride and triethylamine has also been used for effecting the conversion of an alcohol to an olefin. Reaction of **144** with methanesulfonyl chloride and triethylamine in dichloromethane at -15°C afforded an inseparable mixture of compounds **145** and **146** in the ratio of 1 : 1 and in 76% yield. The vinylic protons of **146** could be assigned to the signals at $\delta$ 6.50, 6.40 and 5.70 in the $^1$H NMR spectrum of the mixture. Formation of compound **146** was not unexpected since **144** has two *trans* diaxial protons, at $C_1$ and $C_9$, which could be eliminated.

Another dehydration method reported by Nishiguchi *et al.*[142, 143] utilizes copper(II) sulphate adsorbed on silica gel ($CuSO_4$-$SiO_2$). This catalyst was prepared by mixing chromatographic grade silica gel (230-400 mesh) with aqueous copper(II) sulfate and the water was evaporated by heating under reduced pressure. It was claimed that secondary and tertiary alcohols could be dehydrated under mild conditions. The mechanism of this dehydration reaction is not well understood. Treatment of **144** with $CuSO_4$-$SiO_2$ (1 mmol/g) in refluxing benzene produced an inseparable mixture of **145** and **146** in a ratio of 5 : 2 in 58% yield. Despite the moderate yield obtained, the reaction was relatively clean with no other by-products being produced. Consequently, the crude product obtained from this dehydration reaction was used for the final transformation.

The final step of this synthesis involved the reduction of the enone to an allylic alcohol. This conversion could be effected using sodium borohydride and cerium(III) chloride in methanol.[144, 145] This combination had been reported to be a good reducing agent for the enone system as it selectively reduced the ketone carbonyl only. In addition, sodium borohydride reduces an ester functionality very slowly as compared to a ketone. Reduction of the mixture of compound **145** and **146** in methanol with sodium borohydride and cerium(III) chloride heptahydrate at -78°C for 6 h provided "methyl ledesmate" (**38**) in 43% overall yield from **144**. This compound was obtained as a colorless oil and showed a specific rotation of $[\alpha]_D^{23}$ -77.35° (c. 0.49, $CHCl_3$), which was very different from the reported value of $[\alpha]_D$+7.4° (c. 0.80, $CHCl_3$). In addition, comparision of the $^1H$ NMR spectrum of synthetic **38** with that of natural "methyl ledesmate" (Table 11), clearly indicated that **38** was not the desired natural product.

In order to determine the identity of the final product, the structure and stereochemistry of **38** were established as follows. The IR spectrum showed strong absorptions at 3400 and 1721 $cm^{-1}$ corresponding to a hydroxyl and a conjugated ester respectively. A molecular ion peak at m/z 262.1565, corresponding to the formula $C_{16}H_{22}O_3$ was observed in the mass spectrum. The presence of four vinylic protons in the $^1H$ NMR spectrum indicated that the newly formed double bond was in the $C_9$ position. The hydroxyl proton appeared as a multiplet at $\delta$ 1.42 ($D_2O$ exchangable). Characterization of **38** as its acetate **37** (by treatment of **38** with pyridine and acetic anhydride) showed a downfield shift of $H_3$ from $\delta$ 4.20 to 5.45. Evidence of the stereochemistry of $C_3$ was obtained from extensive $^1H$ decoupling experiments. The α-proton of the hydroxyl group, $H_3$, appeared as a doublet of doublet of multiplets at $\delta$ 4.20. Irradiation of this signal resulted in a simplification of the signal at $\delta$ 2.51 ($H_{2e}$, ddd, $J$ = 12, 6.5,

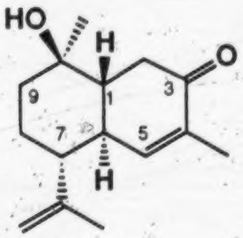
**Table 11**. $^1H$ NMR data of compound **38** and "methyl ledesmate"



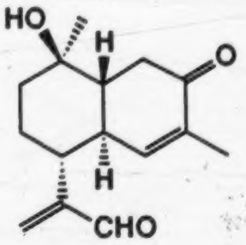
| "Methyl ledesmate" | | Proton | Synthetic **38** | |
|---|---|---|---|---|
| δ (ppm) | (multiplicity; *J* in Hz) | | δ (ppm) | (multiplicity; *J* in Hz) |
| 1.36 | (dd; 10, 8) | $H_2$ | 1.27 | (ddd; 12, 12, 10) |
| 2.38 | (dd; 5, 2) | $H_2$ | 2.51 | (ddd; 12, 6.5, 2) |
| 3.78 | (dd; 8, 5) | $H_3$ | 4.20 | (ddm; 10, 6.5) |
| 5.10 | (br s) | $H_5$ | 5.38 | (m) |
| 2.80 | (ddd; 9, 6, 2) | $H_6$ | 2.37 | (m) |
| 2.60 | (m) | $H_7$ | 2.58 | (ddd; 11, 11, 5.5) |
| | | $H_8$ | 2.20 | (m) |
| | | $H_8$ | 2.10 | (m) |
| 5.10 | (br s) | $H_9$ | 5.38 | (m) |
| 3.10 | (ddd; 10, 9, 2) | $H_1$ | 2.10 | (m) |
| 5.45 | (d; 2) | $H_{1\bar{3}}$ | 5.54 | (s) |
| 6.15 | (d; 2) | $H_{13}$ | 6.30 | (s) |
| 1.65 | (br s) | $H_{11}$ | 1.68 | (br s) |
| | | $H_{15}$ | 1.70 | (m) |
| 3.68 | (s) | $OCH_3$ | 3.74 | (s) |

2 Hz) and 1.27 ($H_{2ax}$, ddd, *J* = 12, 12, 10 Hz). This strongly suggested that $H_3$ was in an axial position which was coupled to the two adjacent methylene protons with coupling constant of 10 and 6.5 Hz. This assignment was further supported by an NOE experiment. When $H_3$ was irradiated, NOE enhancements of 5.7% on $H_{2e}$ and 6.4% on $H_1$ were observed. Also, the stereochemistry of $C_1$, $C_6$ and $C_7$ was later confirmed by an X-ray analysis of "(-)-methyl zafronate". From this data, compound **38** showed the same structure and stereochemistry proposed for the target molecule. The reason for the apparent discrepencies in the spectroscopic data of the natural and the synthetic compounds remains unknown. We wished to compare the spectra of the "authentic" natural product with those of compound **38**. However, attempts to obtain an authentic sample of the natural product or copies of the original spectra from the original investigators failed to produce any response.

We then decided to carry on with the synthesis of (-)-methyl zafronate, which would serve to double check the synthetic route. It was also our intention to eventually determine the structure and stereochemistry by X-ray analysis. The same sequence of reactions was then applied to the isomeric alcohol **138** for the preparation of (-)-methyl zafronate. Treatment of **138** with silver(I) oxide in aqueous methanol under reflux for 20 h provided compound **147**, which had a specific rotation of $[\alpha]_D^{23}$ -53.15° (c. 3.9, $CHCl_3$) in 63% yield. The IR spectrum of this compound showed absorptions at 3440 $cm^{-1}$ due to the hydroxyl group and at 1675 $cm^{-1}$ for the enone system. The mass spectrum displayed a molecular ion peak at m/z 234.1623, corresponding to the molecular formula $C_{15}H_{22}O_2$, and a fragment due to the loss of a $H_2O$ molecule at m/z 216.1517 ($C_{15}H_{20}O$). The absence of the thioacetal unit in the $^1H$ NMR spectrum indicated that dethioacetalization had taken place. The vinylic proton of the enone appeared as a multiplet at δ 6.57. The methylene protons adjacent to the enone carbonyl appeared at δ 2.79 and 2.16, each as a doublet of doublets with a geminal coupling of 16 Hz. The presence of an enone was also confirmed by signals at δ 200.09 (enone carbonyl), 147.06 and 135.30 (vinylic carbons of enone) in the $^{13}C$ NMR spectrum.



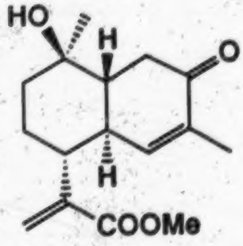
**147**



**148**

Having differentiated the reactivity of the two double bonds of compound **147**, we proceeded to introduce the α,β-unsaturated aldehyde group. When **147** was treated with selenium dioxide in glacial acetic acid from room temperature to 70°C for a period of 15 min, a 44% yield of **148** was obtained. This compound exhibited a specific rotation of $[\alpha]_D^{23}$ -70.90° (c. 0.646, $CHCl_3$) and a molecular ion peak at m/z 248.1414, consistent with the expected molecular formula $C_{15}H_{20}O_3$ in the mass spectrum. It also had two broad absorptions in the IR spectrum, one at 3460 $cm^{-1}$ (hydroxyl) and the other at 1675 $cm^{-1}$ (conjugated ketone and aldehyde). In the $^1H$ NMR spectrum, the aldehydic proton appeared as a singlet at δ 9.62. The β-protons of the conjugated aldehyde appeared at δ 6.38 and 6.23 while the β-proton of the enone appeared at δ 6.27. Previously, allylic oxidation was effected by utilizing selenium dioxide and *tert*-butyl hydroperoxide. When this procedure was employed on compound **147**, the starting material slowly decomposed and no desired product was obtained after 7 days.

The next key compound required was the α,β-unsaturared ester **149** which could be prepared in two steps from **148** by Jones oxidation followed by methylation. Treatment of **148** with chromic acid in acetone followed by methylation of the resulting acid with methyl iodide and anhydrous potassium carbonate afforded **149** in 34% yield. The yield of this reaction was not optimized as this conversion was performed only once.



**149**

Compound **149** showed a specific rotation of $[\alpha]_D^{22}$ -78° (c. 0.7, $CHCl_3$). Two carbonyl absorptions at 1717 (conjugated ester) and 1674 $cm^{-1}$ (conjugated ketone) and a hydroxyl absorption at 3460 $cm^{-1}$ were observed in the IR specturm. In the $^1H$ NMR spectrum, the presence of a conjugated ester was also indicated by a singlet at δ 3.80 (methoxy) and two vinylic β-protons at δ 6.38 and 5.67. The mass spectrum showed a molecular ion peak at m/z 278.1520, in agreement with the required formula $C_{16}H_{22}O_4$.

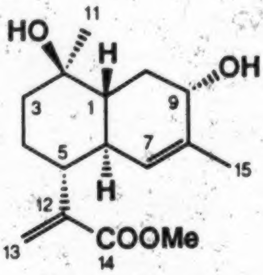
When **149** in methanol was treated with sodium borohydride and cerium(III) chloride heptahydrate at -78°C for 1.3 h, an 85% yield of compound **34** was obtained. Compound **34** showed a close resemblance to natural (-)-methyl zafronate in the mp, specific rotation and IR (Table 12). However, a comparison of the $^1$H NMR spectrum of the synthetic **34** with that of (-)-methyl zafronate (Table13), indicated that **34** was not in fact the desired natural product.

**Table 12**. Spectral data of **34** and "methyl zafronate"

| | Synthetic **34** | "Methyl zafronate" |
|---|---|---|
| mp | 185-186°C | 181-182°C |
| specific rotation | -97.5° (c. 0.44, EtOH) | -77.5° (c. 1.6, EtOH) |
| IR | 3328, 1716 cm$^{-1}$ | 3330, 1725 cm$^{-1}$ |

Due to the complexity of the $^1$H NMR spectrum of compound **34**, $^1$H decoupling experiments only allowed the assignment of the protons but not the stereochemistry of $C_9$. Consequently, the stereochemistry of $C_2$, which was assigned by comparison with known compounds, and $C_9$ could not be unambiguously determined. Fortunately, recrystallization of this compound from acetone produced colorless needle shaped crystals which were

**Table 13**. ${}^1H$ NMR data of **34** and "methyl zafronate"



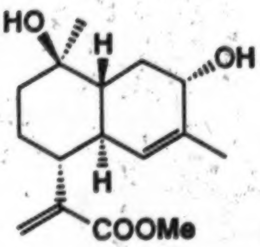
| Natural |  | Proton | Synthetic |  |
|---|---|---|---|---|
| δ (ppm) | (multiplicity; *J* in Hz) |  | δ (ppm) | (multiplicity; *J* in Hz) |
| 6.18 | (d; 2) | $H_{13}$ | 6.30 | (d; 1) |
| 5.60 | (d; 2) | $H_{13}$ | 5.57 | (s) |
| 5.10 | (br s) | $H_7$ | 5.23 | (m) |
| 3.90 | (dd; 8, 6) | $H_9$ | 4.20 | (m) |
| 3.65 | (s) | $OCH_3$ | 3.77 | (s) |
| 2.36 | (dd; 6, 2) | $H_{10}$ | 2.40 | (ddd; 12, 6, 2) |
| 2.30 | (m) | $H_5$ | 2.23 | (m) |
| 2.60 | (ddd; 10, 9, 1.5) | $H_6$ |  |  |
| 1.63 | (br s) | $H_{15}$ | 1.70 | (br s) |
|  |  | OH | 1.77 | (m) |
| 1.34 | (m) | $H_4$ |  |  |
|  |  | $H_4$ | 1.22-1.56 | (m) |
|  |  | $H_3$ |  |  |
|  |  | $H_3$ |  |  |
| 2.10 | (ddd; 10, 10, 2) | $H_1$ |  |  |
|  |  | OH |  |  |
| 1.40 | (dd; 10, 8) | $H_{10}$ |  |  |
| 1.13 | (s) | $H_{11}$ | 1.21 | (s) |

suitable for X-ray diffraction analysis. Figure 4 clearly showed the *trans*, *trans*-relationship between $H_1$, $H_6$ and $H_5$, the $C_2$ stereochemistry with β-hydroxyl group and the α-orientated hydroxyl group at $C_9$. This allowed us to confirm unambiguously that compound **34** had the structure and stereochemistry proposed for the target molecule.

Attempts to determine the optical purity of compound **34** using (+)-Eu(hfc)$_3$ failed to produce any splitting of the signals in the high resolution $^1$H NMR spectrum. This observation could result from either that the chiral shift reagent was unsuitable or that the compound was already optically pure within experimental limits.

## IV. STUDIES TOWARDS THE TOTAL SYNTHESIS OF (+)-ARTEMISININ

Ketone **79** was envisioned as a suitable intermediate for the synthesis of (+)-artemisinin as it was suitably functioned for a rapid conversion to the key intermediate **81** (Scheme 6). In addition, **79** had the required stereogenic centers $C_1$ and $C_5$ which were confirmed by X-ray analysis. The functional group transformation involved three major operations. First, the introduction of a carbon functionality to $C_2$ stereoselectively. Second, the conversion of the isopropenyl group to 1-carbomethoxyethyl and finally the removal of the thioacetal or oxygen equivalent from the cyclohexene ring system.



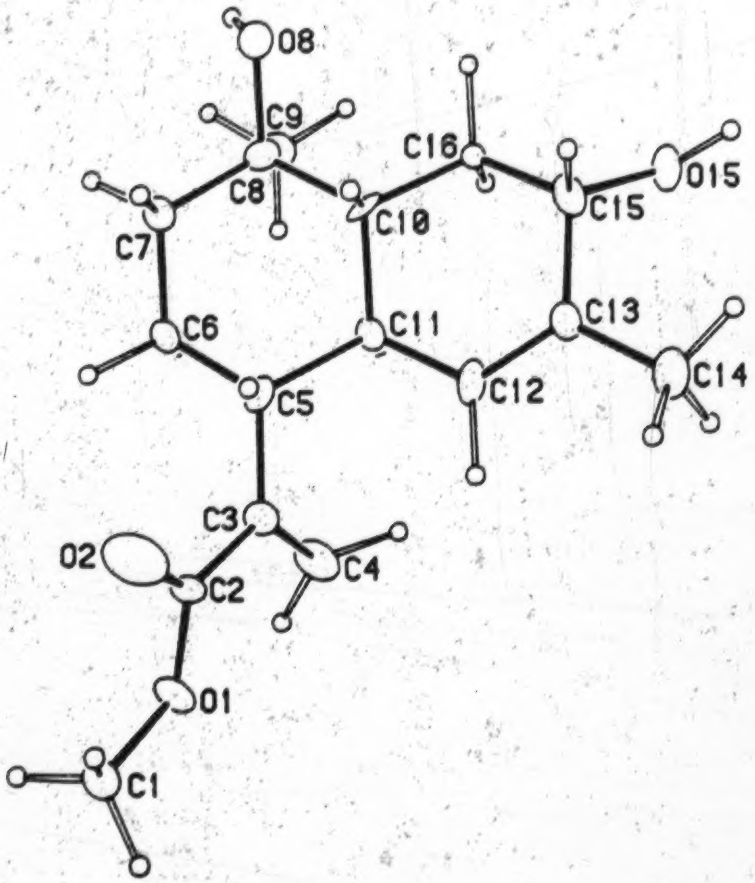
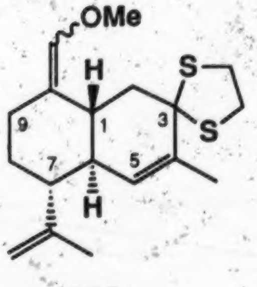


**Figure 4**. The three dimensional X-ray crystallographical structure of compound **34**

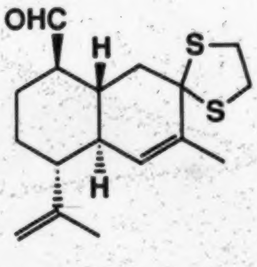
Examination of the conformation of compound **44** indicated that the methyl group of the cyclohexane ring was equatorial, which is thermodynamically more stable than the axial methyl group. In order to control this stereochemistry, the methyl group was introduced *via* the aldehyde functionality, whereby the $\alpha$-proton could be epimerized. This aldehyde could be prepared by Wittig reaction followed by hydrolysis of the enol ether.[146]

Reaction of **79** in benzene with methoxymethylenetriphenylphosphorane (which was prepared from the reaction of dimethylsulfinyl carbanion with methoxymethyltriphenylphosphonium chloride) at room temperature produced a 94% yield of enol ether **150**. This compound consisted of two stereoisomers of the vinylic methoxy group, which were not separated as they would be destroyed in the subsequent step. The presence of the enol ether function was indicated by singlets at $\delta$ 5.68 (vinylic proton of the enol ether) and 3.58 (methoxy) for the major isomer and by singlets at $\delta$ 5.76 (vinylic proton of the enol ether) and 3.49 (methoxy) for the minor isomer in the $^1$H NMR spectrum. The absence of a ketone carbonyl absorption band in the IR spectrum confirmed that the transformation had taken place. The mass spectrum showed a molecular ion peak at m/z 322.1423, which was in agreement with the expected formula $C_{16}H_{26}OS_2$.

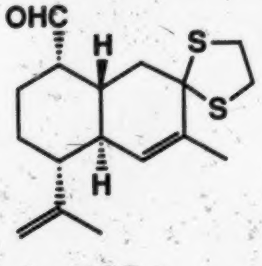


**150**

Initially, hydrolysis of the enol ether was attempted using perchloric acid in aqueous THF. Under these conditions, the rate of hydrolysis was slow and the product decomposed before all the starting material had been consumed. Milder reaction conditions were then employed. Treatment of enol ether with *p*-toluenesulfonic acid (0.2 eq) in refluxing aqueous acetone for 10 h afforded a mixture of aldehydes **151** and **152** in the ratio of 35 : 65. The undesired kinetic product, **152** which contains an axial aldehyde group was found to be the major isomer, it was expected that epimerization of this compound would give the desired thermodynamically more stable equatorial aldehyde **151**. Thus, the mixture of aldehydes was epimerized with sodium hydroxide in aqueous methanol at room temperature for 24 h which produced an equilibrium mixture of **151** and **152** in the ratio of 93 : 7, respectively.



**151**

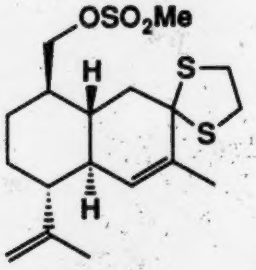


**152**

Aldehyde **151** displayed a single carbonyl absorption at 1725 $cm^{-1}$ in the IR spectrum. In the $^1H$ NMR spectrum, the aldehydic proton appeared as a doublet at $\delta$ 9.58, indicating that the enol ether had been hydrolyzed. The presence of aldehyde group was confirmed by a signal at $\delta$ 204.61 in the $^{13}C$ NMR APT spectrum. The molecular ion of this compound was found in the mass spectrum at m/z 308.1269, which was in agreement with the formula $C_{17}H_{24}OS_2$.

With aldehyde **151** in hand, the next objective was the conversion of the aldehyde carbonyl to a methyl group. There are a number of methods available to effect such a transformation.[147-150] An attempt to achieve this conversion by the Wolff-Kishner reduction,[151] in which **151** was treated with hydrazine and anhydrous potassium carbonate in diethylene glycol at 180°C, resulted in extensive decomposition of the molecule with the loss of the thioacetal unit.

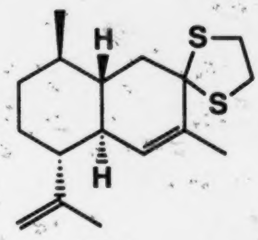
We therefore turned our attention towards milder methods for the complete reduction of the carbonyl group. One such method involved the conversion of the aldehyde carbonyl to its thioacetal followed by treatment with Raney nickel.[118, 152, 153] This could not be attempted since a thioacetal unit was already present in **151**. Another method involving the alcohol derivative of the aldehyde was then employed. Reduction of aldehyde **151** in THF with lithium aluminium hydride under reflux conditions gave the corresponding primary alcohol. The presence of a hydroxyl group was indicated by a broad absorption at 3360 cm$^{-1}$ in the IR spectrum. This primary alcohol was then converted to the sulfonate ester by treating the crude alcohol with methanesulfonyl chloride and triethylamine in dichloromethane at 0°C giving compound **153** in an overall yield of 92%. The reason for the introduction of the mesylate group to the primary alcohol was due to the fact that it could be readily reduced to the corresponding alkane.[154]



**153**

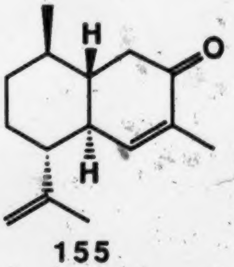
Compound **153** was obtained as a single diastereomer (mp 119-120°C) after recrystallization (3 x) from dichloromethane-petroleum ether. A specific rotation of $[\alpha]_D^{23}$ -31.88 (c. 1.38, $CHCl_3$) was displayed by this compound. The absence of a hydroxyl absorption in the IR spectrum suggested that the conversion had in fact taken place. The $^1$H NMR spectrum showed signals for the two α-methylene protons of the mesylate group at δ 4.28 and 4.23, each as a doublet of doublets, and the methyl of the mesylate group appeared as a singlet at δ 3.06. The mass spectrum showed a molecular ion peak at m/z 388.1193, corresponding to the formula $C_{18}H_{28}O_3S_3$.

Reduction of the mesylate group to methyl was achieved by treatment of **153** with lithium aluminium hydride in refluxing THF for 1 h. After chromatographic purification, compound **154** was obtained in 91% yield. This compound displayed a specific rotation of $[\alpha]_D^{23}$ -29.17 (c. 0.84, $CHCl_3$) and a molecular ion peak at m/z 294.1476, consistent with the formula $C_{17}H_{26}S_2$ in the mass spectrum. In the $^1H$ NMR spectrum, the trisubstituted and disubstituted vinylic methyls appeared as a doublet of doublets at δ 1.93 and as a broad singlet at δ 1.65 respectively. The remaining methyl appeared at δ 0.95 as a doublet.



**154**

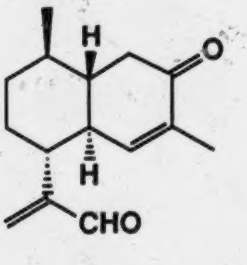
Having converted the aldehyde carbonyl into a methyl group, the next operation involved the transformation of the isopropenyl side chain into 1-carbomethoxyethyl. Prior to this transformation, the thioacetal unit had to be removed. This was achieved by using mercury(II) chloride. Treatment of compound **154** with mercury(II) chloride in 80% aqueous acetonitrile provided enone **155** in 89% yield.



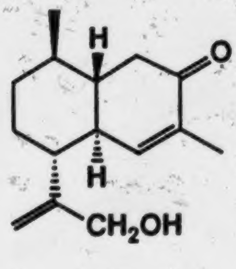
**155**

Compound **155** displayed a specific rotation of $[\alpha]_D^{23}$ -69.44° (c. 1.26, $CHCl_3$) and an absorption at 1677 $cm^{-1}$ (due to the carbonyl of the enone) in the IR spectrum. The $^1H$ NMR spectrum showed a signal at $\delta$ 6.63, which was assigned to the β-enone proton, and signals at $\delta$ 2.76 and 2.02 were assigned to the two methylene protons adjacent to the enone carbonyl. The presence of the enone system was confirmed by signals at $\delta$ 200.34 (enone carbonyl), 148.53 and 135.26 (vinylic carbons of the enone) in the $^{13}C$ NMR APT spectrum. In the mass spectrum, a molecular ion peak at m/z 218.1668 was observed, corresponding to the formula $C_{15}H_{22}O$.

With the required key intermediate **155** in hand, the next step was the introduction of an oxygen funtionality at the allylic position. A mixture of selenium dioxide and *tert*-butyl hydroperoxide was employed for this purpose. Reaction of **155** in dichloromethane with selenium dioxide, in the presence of *tert*-butyl hydroperoxide and a trace amount of glacial acetic acid for 6 days at room temperature gave compounds **156** and **157** in 73% combined yield.



**156**

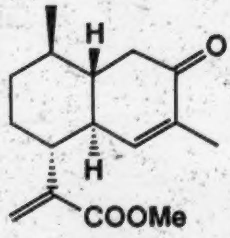


**157**

Compound **156** displayed a specific rotation of $[\alpha]_D^{22}$ -99.63° (c. 1.08, $CHCl_3$) and a molecular ion peak at m/z 232.1461, in agreement with the expected formula $C_{15}H_{20}O_2$, in the mass spectrum. The IR spectrum indicated the presence of conjugated carbonyls by absorption bands at 1688 and 1674 $cm^{-1}$. The signals at $\delta$ 9.62, 6.35 and 6.20 in the $^1H$ NMR spectrum were attributed to the protons of the $\alpha,\beta$-unsaturated aldehyde group.

A specific rotation of $[\alpha]_D^{23}$ -105.59 (c. 3.94, $CHCl_3$) was displayed by compound **157**. In its IR spectrum, strong hydroxyl and carbonyl absorptions were observed at 3452 and 1672 $cm^{-1}$ respectively. In the $^1H$ NMR spectrum, the two protons $\alpha$ to the hydroxyl group appeared at $\delta$ 4.15 as a broad singlet, while the two vinylic protons appeared at $\delta$ 5.26 and 4.98. The presence of a carbon bearing the hydroxyl group was confirmed by a signal at $\delta$ 64.98 in the $^{13}C$ NMR APT spectrum. A molecular ion peak at m/z 234.1621, consistent with the formula $C_{15}H_{22}O_2$, was observed in the mass spectrum.

The allylic alcohol **157** together with compound **156** could be oxidized to the acid in a single step by Jones oxidation. Treatment of **156** and **157** with chromic acid in acetone provided a single acid. This crude acid was methylated with methyl iodide and anhydrous potassium carbonate in acetone to give compound **158** in 49% yield over two steps.

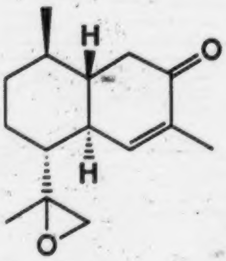


**158**

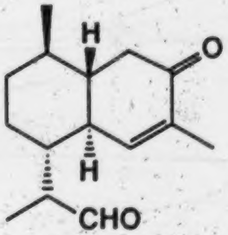
This compound, which was obtained as a colorless oil after flash chromatography, displayed a specific rotation of $[\alpha]_D^{22}$ -102.5° (c. 2.76, $CHCl_3$). The presence of a conjugated ester was indicated by the signals at δ 3.80 (methoxy), 6.36 and 5.62 (β-vinylic protons) in the $^1H$ NMR spectrum. This was further confirmed by the IR spectrum, which showed carbonyl absorptions at 1720 and 1676 $cm^{-1}$ corresponding to a conjugated ester and cojugated ketone, respectively. The mass spectrum supported the assignment of this structure showing a molecular ion peak at m/z 262.1565, corresponding to the formula $C_{16}H_{22}O_3$.

Although compound **155** could be smoothly converted to **158** in three steps, the α,β-unsaturated ester group in intermediate **158** still had to be selectively reduced to the saturated ester. However, this reduction step could be eliminated if the oxygen functionality was introduced by epoxidation followed by rearrangement of the epoxide to the aldehyde. It was known that epoxides could rearrange to an aldehyde or a ketone when treated with a Lewis acid such as boron trifluoride etherate.[155]

Treatment of **155** in dichloromethane with *m*-chloroperoxybenzoic acid at 0°C for 10 h provided a 1 : 1.7 (from $^1H$ NMR) mixture of epimeric epoxides **159** in 91% yield. This mixture showed an enone absorption at 1675 cm$^{-1}$ in the IR spectrum. A molecular ion peak at m/z 234.1618, in agreement with the formula $C_{15}H_{22}O_2$, was observed in the mass spectrum. In the $^1H$ NMR spectrum, the disappearance of the vinylic protons of the isopropenyl side chain indicated that epoxidation had taken place.



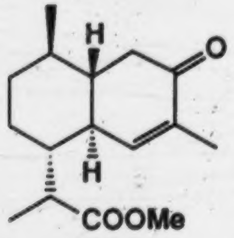
**159**



**160**

Conversion of epoxide **159** to the aldehyde was effected by treatment of **159** in dichloromethane with boron trifluoride etherate at 0°C for 10 min. After chromatographic purification, a mixture of two diastereomers of **160** in a ratio of 1 : 2.2 (by $^1H$ NMR) was obtained in 81% yield. The rearrangement occurred rapidly and was difficult to monitor by TLC as the starting material and **160** had the same $R_f$. Initial attempts to monitor the rearrangement by TLC led to the erroneous assumption that no reaction had in fact occurred. Prolonged reaction times resulted in the eventual decomposition of the rearranged products.

Compound **160**, which consisted of two diastereoisomers (1 : 2.2), appeared as one spot on a TLC plate and could not be separated by flash chromatography. In the $^1H$ NMR spectrum, two sets of signals that corresponded to the two diastereomers were observed. The formation of an aldehyde was confirmed by the appearance of signals for the aldehydic proton, a doublet at δ9.84 and a singlet at δ 9.71 for the minor and major isomers respectively. The IR spectrum displayed carbonyl bands at 1721 and 1674 cm$^{-1}$ corresponding to an aldehyde and conjugated ketone, respectively. The mass spectrum showed a molecular ion peak at m/z 234.1620, in accordance with the formula $C_{15}H_{22}O_2$.



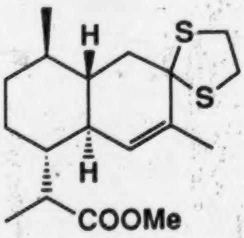
**161**

Transformation of **160** to the required ester **161** for this (+)-artemisinin synthesis, was achieved as described previously for **156** and **157**. The 1 : 2.2 mixture of aldehydes was oxidized to the corresponding acid by chromic acid. The resulting acid was then esterified in acetone with methyl iodide and potassium carbonate to give a 1 : 3.6 mixture of ester **161** in 69% yield. When DMSO was used as the solvent, the same yield of **161** was obtained. Attempts to separate the mixture by flash chromatography were unsuccessful. However, the major isomer could be obtained by recrystallization from dichloromethane-petroleum ether in the pure form. The presence of an ester functionality was indicated by singlets at δ3.72 (major) and 3.70 (minor) for the methoxy group in the $^1$H NMR spectrum. This was further confirmed by the IR spectrum, which showed carbonyl absorptions at 1727 (ester) and 1663 $cm^{-1}$ (conjugated ketone). The mass spectrum showed a molecular ion peak at m/z 264.1724, consistent with the expected formula $C_{16}H_{24}O_3$.

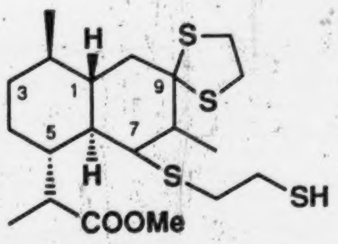
At this stage, it should be mentioned that the stereogenic center, $C_{12}$, of the side chain could not be determined by spectroscopic method. It was thought that the correct stereochemistry could be determined after the ozonolysis of compound **81**. So, we then focussed our attention on the preparation of this compound.

The next stage of the synthesis called for the removal of the enone carbonyl. Initially, the direct single step conversion of carbonyl to methylene using boron trifluoride etherate and trimethylsilane[156] was attempted. Unfortunately, a mixture of six unidentified compounds was obtained. One possible explanation for this could be that both the carbonyl and the double bond were reduced during the reaction.

We then tried a milder method involving two steps. This method involved the initial conversion of the ketone to its corresponding thioacetal, followed by treatment with Raney nickel. When **161** (a mixture of 1 : 4.7) in dichloromethane was treated with 1,2-ethanedithiol and boron trifluoride etherate at -10°C for 43 h, a 1 : 4.7 mixture of thioacetals **162** was obtained in 30% yield together with the by-product **163** which was isolated in 36% yield. The formation of thioacetal **162** was confirmed by the appearance of four-proton multiplet at $\delta$ 3.31 in the $^1$H NMR spectrum and the absence of an enone carbonyl absorption in the IR spectrum. In the mass spectrum, a molecular ion peak at m/z 340.1524, corresponding to the formula $C_{18}H_{28}O_2S_2$, was observed.



**162**

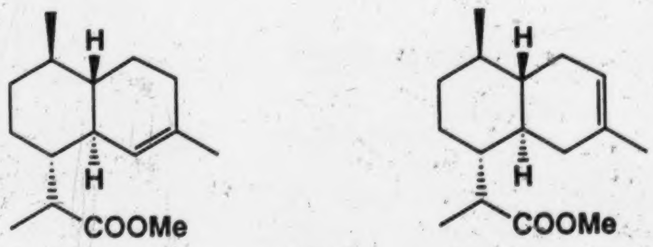


**163**

The IR spectrum of compound **163** showed the presence of an ester carbonyl band at 1734 cm$^{-1}$ and the disappearance of the enone carbonyl absorption. In the $^1$H NMR spectrum, no vinylic proton signal was observed, which suggested the 1,4-addition of 1,2-ethanedithiol to the enone. Further evidence of the formation of **163** came from the mass spectrum, which showed a molecular ion peak at m/z 434.1446, which was in agreement with the formula $C_{20}H_{34}O_2S_4$.

Under these reaction conditions (boron trifluoride etherate and 1,2-ethanedithiol), the 1,4-addition of 1,2-ethanedithiol can readily compete with the thioacetalization reaction. In order to improve the yield of the desired compound **162**, we turned our attention to alternative methods of making the thioacetal.[157] The method which we tried involved the use of *p*-toluenesulfonic acid and 1,2-ethanedithiol in refluxing benzene. When **161** was added to a mixture of 1,2-ethanedithiol and *p*-toluenesulfonic acid in refluxing benzene, **162** was obtained in 65% yield; none of compound **163** was isolated.

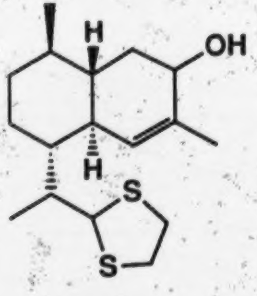
Desulfurization of the mixture of thioacetals **162** was achieved with Raney nickel (grade W-2) in ethanol at room temperature. After purification by flash chromatography, **164** (a 1 : 2 : 2 : 3 (by $^1$H NMR) mixture of four compounds) was obtained in 60% yield. The $^1$H NMR spectrum showed the disappearance of the thioacetal unit. Signals for the vinylic protons appeared at δ 5.51 and 5.39. The IR spectrum showed the presence of an ester carbonyl at 1737 cm$^{-1}$. The mass spectrum displayed a molecular ion peak at m/z 250.1927, which was consistent with the formula $C_{16}H_{26}O_2$.



**164**

Evidently, migration of the double bond occurred during this desulfurization reaction (probably by the formation of an allylic radical) to the $C_3$ position to give two undesired products. At this stage, it was thought that probably an $S_N2$ displacement of an alcohol derivative might prevent or reduce the formation of the $\Delta^{3,4}$ isomers. Consequently, the sequence of operations in this synthesis had to be changed. The introduction of the ester functionality to the side chain could be done after the reduction of the carbonyl function to a methylene group.

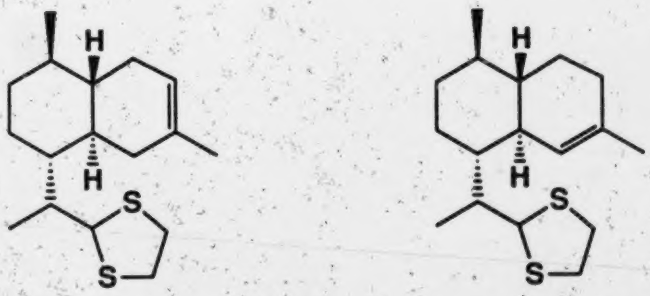
We started this new synthetic route with compound **159**. Previously, we had shown that the epoxide rearranged to an aldehyde when it was treated with boron trifluoride etherate. It was thought that in the presence of 1,2-ethanedithiol, the aldehyde function would be protected as a thioacetal. A mixture of epimeric epoxides **159** (1 : 1.7) in dichloromethane was treated with 1,2-ethanedithiol and boron trifluoride etherate at 0°C. The reaction was complete within 5 min. A crude product was obtained which indicated the presence of a thioacetal moiety at δ 3.23 and β-enone protons at δ 6.86 (minor) and 6.80 (major) in its $^1H$ NMR spectrum.



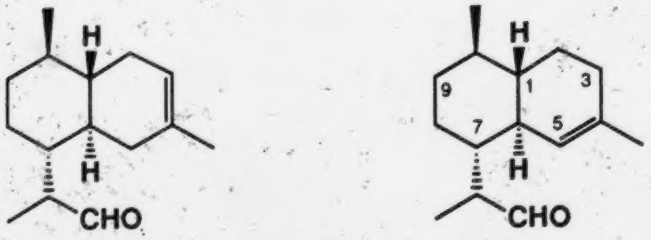
**165**

The crude thioacetal was then reduced with sodium borohydride and cerium(III) chloride in methanol to give a 1 : 2.5 mixture of **165** in an overall yield of 57% from **159**. Although this mixture could not be separated by flash chromatography, a 92 : 8 mixture could be obtained by recrystallization from dichloromethane-petroleum ether. This mixture showed a broad hydroxyl absorption at 3380 $cm^{-1}$ in the IR spectrum. A molecular ion peak at m/z 312.1573, consistent with the formula $C_{17}H_{28}OS_2$, was observed in the mass spectrum. The presence of a thioacetal was indicated by the appearance of a four-proton multiplet at $\delta$ 3.22 in the $^1$H NMR spectrum. A signal at $\delta$ 4.15 indicated the presence of the $\alpha$-proton of hydroxyl group.

With compound **165** in hand, we proceeded to make its mesylate derivative. Mesylation of **165** (1 : 1.6) with methanesulfonyl chloride and triethylamine produced a crude product. This allylic mesylate was not purified as it was thought that it might decompose during flash chromatography (we had previously experienced such a decomposition with a similar allylic compound). Thus the crude product was reduced by lithium aluminium hydride in THF. However, after purification, a 13 : 12 : 7 mixture of compounds **166** was obtained in 76% yield. The $^1$H NMR spectrum of this mixture showed signals for vinylic protons at $\delta$ 5.50, 5.45 and 5.37 (in the ratio of 13 : 12 : 7, respectively). The thioacetal unit appeared at $\delta$ 3.21. The mass spectrum showed a molecular ion peak at m/z 296.1634, which corresponded to the formula $C_{17}H_{28}S_2$. As before, some undesired $\Delta^{3,4}$ product was obtained, in this case, from the $S_N2'$ reaction. Further investigation of this reaction is required in order to prevent the migration of the double bond.



**166**



**167**

Despite the somewhat disappointing results of the reduction reaction, we nonetheless decided to carry out the next transformation. Dethioacetalization of **166** with mercury(II) chloride gave a 24% yield of a 2 : 7 : 3 : 7 mixture of **167**. The $^1H$ NMR spectrum indicated the presence of an aldehyde with signals at $\delta$ 9.83, 9.82, 9.80 and 9.67 (integral ratio of 2 : 7 : 3 : 7, respectively). This was confirmed by the IR spectrum, which showed a carbonyl absorption at 1722 $cm^{-1}$. A molecular ion peak at m/z 220.1826, in agreement with the required formula $C_{15}H_{24}O$, was observed in the mass spectrum. It would appear that this procedure is not suitable for the dethioacetalization. Other milder methods should be investigated, for example, those using mercury(II) oxide and boron trifluoride etherate,[158] and wet $SOCl_2$-$SiO_2$.[159]

In order to complete the synthesis, the key intermediate **80** has yet to be prepared. This could be achieved by the ozonolysis of **164**. This work is currently in progress.

# EXPERIMENTAL

## General

All melting points were determined on a Kofler hot stage apparatus and are uncorrected. Elemental analysis were performed by the microanalytical laboratory of this department. Infrared spectra (IR) were recorded on a Perkin-Elmer model 457 or Nicolet 7-119 FT-IR spectrometer and were normally obtained in chloroform cast unless otherwise stated. High resolution mass spectra (HRMS) were obtained using a Kratos AEI MS-50 high resolution mass spectrometer. Chemical ionization mass spectra (CIMS) were obtained using an AEI MS-12 mass spectrometer, with ammonia as the reagent gas. Proton nuclear magnetic resonance spectra ($^1$H NMR) were recorded on Bruker WH-300 (300 MHz) and WH-400 (400 MHz) spectrometers and were obtained from solution in deuteriochloroform using tetramethylsilane as an internal reference. Coupling constants are reported to within ± 0.5 Hz. Chemical shift measurements were reported in ppm downfield from TMS in delta ($\delta$) units. The following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, ax = axial, e = equatorial. Carbon-13 nuclear magnetic resonance spectra ($^{13}$C NMR) were recorded on a Bruker WH-300 (75 MHz). Carbon-13 multiplicities were derived from off-resonance or Carr-Purcel-Meiboom-Gill spin echo J-modulated experiments (APT or Attached Proton Test). Methyl and methine groups were shown as signals possessing an antiphase (a) with respect to the deuteriochloroform signal, whereas methylene groups, quaternary carbon atoms and carbonyl groups appeared in phase (p) with it. Nuclear Overhauser Enhancement (NOE) experiments were determined in the difference mode in which a control (undecoupled) spectrum was computer-subtracted from the irradiated spectrum after Fourier transformation. Positive enhancements are defined as signals possessing antiphase with respect to the irradiated signal. Samples for NOE measurements were deoxygenated with argon gas for 5-10 min. Optical rotations were determined in a Perkin-Elmer 241 polarimeter. Specific rotations, $[\alpha]_D$ were reported in degrees at the specified temperature and concentration (c.) was given in grams per 100 ml in the specified solvent.

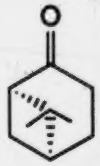
All reactions were carried out under a positive pressure of argon gas. Argon was passed through a column of 4A molecular sieves and a self indicating silica gel. All reactions were monitored by analytical thin-layer chromatography (TLC) on silica gel. The visualization of the chromatograms was completed either by dipping in an ethanol solution of vanillin (5%, w/v) or an aqueous solution of phosphomolybdic acid (3%, w/v). Solvents were removed under reduced pressure on a rotary evaporator. Purification and separation of product mixtures were carried out using flash chromatography on silica gel (230-400 mesh) developed by Still.[160]

## Materials

The anhydrous solvents used were distilled under an argon atmosphere. Diethyl ether, tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME) were dried with sodium and benzophenone. Dichloromethane, pyridine, triethylamine and dimethyl sulfoxide were distilled from calcium hydride. Benzene was distilled from lithium aluminium hydride. Anhydrous $ZnCl_2$ was fused or vacuum dried before used. Unless otherwise stated, anhydrous magnesium sulfate was used for drying organic solutions.

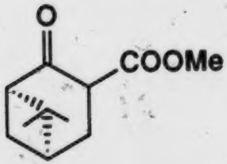
## I. DIELS-ALDER REACTIONS OF ENONE ESTER 27

### (1R, 5S)-(+)-6,6-Dimethylbicyclo[3.1.1]hept-2-one (83)



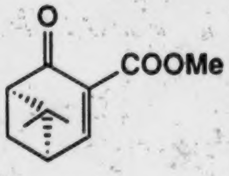
At -78°C, ozone was passed through a solution of (1S, 5S)-(-)-β-pinene (39.17 g, 0.288 mol) in 386 ml of $CH_2Cl_2$ : MeOH (1 : 1). After 6 h, a persistent blue color appeared and the reaction was stopped. Excess ozone was purged with oxygen for 10 min and dimethyl sulfide (25.33 ml) was added to the reaction mixture at -78°C. The mixture was stirred overnight at room temperature and the solvent was removed under reduced pressure on a rotary evaporator. Flash chromatography of the residue on silica gel with 0-10% ether in petroleum ether gave 24.29 g of pure **83** as a colorless oil and also 10.00 g of impure **83**. The impure product was chromatographed again as before to give another 6.61 g of **83** (total yield 30.90 g, 0.244 mol, 78% yield) : $[\alpha]_D^{23}$ = + 16.5° (neat); $^1H$ NMR (300 MHz, $CDCl_3$) δ 2.48-2.66 (m, 3H), 2.34 (ddd, 1H, *J* = 19, 9, 2.5 Hz), 2.24 (m, 1H), 1.88-2.12 (m, 2H), 1.59 (d, 1H, $J = 10$ Hz), 1.33 (s, 3H, *exo* $CH_3$), 0.85 (s, 3H, *endo* $CH_3$); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 214.86 (C=O), 57.96 (CHC=O), 41.18 ($CMe_2$), 40.39 ($CHCMe_2$), 32.77 ($CH_2C$=O), 25.88 (*exo* $CH_3$), 25.24 ($CH_2$), 22.09 (*endo* $CH_3$), 21.38 ($CH_2$); FT-IR 1715 (C=O) $cm^{-1}$; HRMS $M^+$ 138.1046 (calcd. for $C_9H_{14}O$: 138.1045).

### (1R, 5R)-3-Carbomethoxy-6,6-dimethylbicyclo[3.1.1]heptan-2-one (84)



Sodium hydride (80% dispersion in oil, 4.04 g, 0.168 mol, washed with petroleum ether and DME) was suspended in DME (60 ml) under an atmosphere of argon and dimethyl carbonate (30.28 g, 0.336 mol) was added. The suspension was heated under reflux while stirring with a mechanical stirrer. A solution of 9.29 g (0.0673 mol) of nopinone in DME (22 ml) was added dropwise. Heating was continued for 6 h and the mixture was then cooled to 0°C. An aqueous solution of 10% acetic acid was then added with stirring until the pH of the solution was acidic. The mixture was extracted with ether (3 x 70 ml). The extracts were washed with water, saturated aqueous sodium bicarbonate, water and saturated aqueous sodium chloride, dried, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 0-4% ether in petroleum ether gave keto ester **84** (12.41 g, 0.063 mol, 94% yield) as a light yellow liquid which crystallized on standing. This compound existed as a 1 : 1 : 2 mixture: $^1$H NMR (300 MHz, $CDCl_3$) δ 11.94 (br s, C=COH), 3.77, 3.76, 3.61 (s, $OCH_3$), 1.35, 1.33 (s, *exo* $CH_3$), 0.95, 0.88, 0.87 (s, *endo* $CH_3$); FT-IR 1739 (ester, C=O), 1704 (ketone, C=O) $cm^{-1}$; HRMS $M^+$ 196.1105 (calcd. for $C_{11}H_{16}O_3$: 196.1100). Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.31; H, 8.22; found: C, 67.48; H, 8.12.

### (1R, 5R)-(+)-3-Carbomethoxy-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (27)



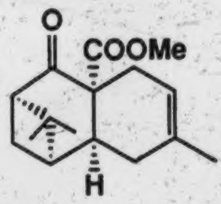
Pyridine (1.39 ml, 0.0172 mol) was added to a solution of phenylselenenyl chloride (3.70 g, 0.0193 mol) in dichloromethane (99.72 ml) at 0°C under an argon atmosphere. After stirring for 10 min, keto ester **84** (3.07 g, 0.0157 mol) in 15.5 ml of dichloromethane was added. After 4 h, the reaction mixture was washed with 1 *M* hydrochloric acid (2 x 50 ml). The organic solution was placed in a flask and cooled to 0°C. An aliquot (1.7 ml) of 30% aqueous hydrogen peroxide solution was added. After stirring for 10 min, an additional 1.7 ml of 30% aqueous hydrogen peroxide was added. After 1 h, 50 ml of aqueous sodium bisulfite solution was added and the layers were separated. The organic layer was washed with saturated aqueous sodium bicarbonate, dried, filtered and concentrated. Flash chromatography of the residue on silica gel eluting with 2-30% ether in

petroleum ether gave **27** (2.68 g, 0.0138 mol, 88% yield) as a colorless oil: $[\alpha]_D^{23}$ = +229.83° (c. 1.15, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) δ 8.40 (dd, 1H, =C**H**), 3.84 (s, 3H, OC**H**$_3$), 2.77-2.93 (m, 3H), 2.14 (d, 1H, O=CCHCH**H**$_{endo}$, *J* = 9 Hz), 1.54 (s, 3H, *exo* C**H**$_3$), 1.04 (s, 3H, *endo* C**H**$_3$); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 197.79 (C=O), 165.57 (=CH), 164.10 (OC=O), 127.93 (=C), 58.76 (CH), 54.76 (C), 51.92 ($OCH_3$), 44.19 (CH), 40.23 ($CH_2$), 26.47, 22.30 (2 x $CH_3$); FT-IR 1747, 1714, 1698 (C=O) $cm^{-1}$; HRMS $M^+$ 194.0946 (calcd. for $C_{11}H_{14}O_3$: 194.0943). Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.01; H, 7.27; found: C, 67.91; H, 7.37.

The Diels-Alder reactions were carried out using the general procedure illustrated below with isoprene for $BF_3{\cdot}OEt_2$, $SnCl_4$ and $FeCl_3$ catalyzed reactions and *trans*-2-methyl-1,3-pentadiene for $ZnCl_2$ catalyzed reactions. Temperatures and times of the reactions as well as the quantities of dienes and Lewis acids relative to **27** can be found in Tables 1 and 2.

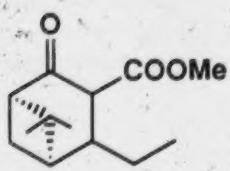
### $BF_3{\cdot}OEt_2$, $SnCl_4$ and $FeCl_3$ catalyzed reactions

**(1R, 3R, 8S, 9R)-(+)-3-Carbomethoxy-6,10,10-trimethyltricyclo-[7.1.1.0$^{3,8}$]undec-5-en-2-one (85)**

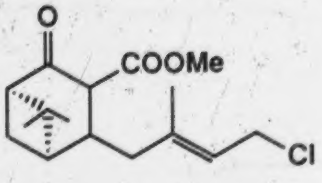


To a solution of **27** (104.3 mg, 0.538 mmol) and 1.08 ml (10.8 mmol) of isoprene in ether (3.90 ml) at -20°C was added 63 µl of $SnCl_4$ under an atmosphere of argon. After stirring for 3 h, 3 ml of saturated aqueous sodium bicarbonate solution was added. The mixture was extracted with ether and the extracts were washed with water, dried, filtered and concentrated. Flash chromatography on silica gel with 2-3% ether in petroleum ether as eluant gave **85** (77.6 mg, 0.296 mmol, 55% yield) as a colorless oil: $[\alpha]_D^{23} = +54.20°$ (c. 1.12, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.48 (m, 1H, C=C**H**), 3.75 (s, 3H, $\mathrm{OC}\mathbf{H}_3$), 3.20 (dddd, 1H, CHC**H**, *J* = 8, 8, 1.5, 1.5 Hz), 3.05 (dd, 1H, $=\mathrm{CHC}\mathbf{H}_e\mathrm{H}$, *J* = 15.5, 6 Hz), 2.66 (dd, 1H, O=CC**H**, *J* = 5.5, 5.5 Hz), 2.47 (dddd, 1H, $\mathrm{CHC}\mathbf{H}_{exo}\mathrm{H}$, *J* = 11, 7, 5.5, 1.5 Hz), 2.15 (m, 3H, $\mathrm{C(CH_3)_2C}\mathbf{H}$, $=\mathrm{CHCH}\mathbf{H}_{ax}$, $\mathrm{C}\mathbf{H}_e\mathrm{HC(CH_3)}=$), 1.95 (d, 1H, $\mathrm{CHCH}\mathbf{H}_{endo}$, *J* = 11 Hz), 1.87 (m, 1H, $\mathrm{CH}\mathbf{H}_{ax}\mathrm{C(CH_3)}=$), 1.72 (br s, 3H, $=\mathrm{CC}\mathbf{H}_3$), 1.34 (s, 3H, *exo* $\mathrm{C}\mathbf{H}_3$), 0.97 (s, 3H, *endo* $\mathrm{C}\mathbf{H}_3$); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 209.83 (C=O), 172.51 (OC=O), 136.76 (C=), 118.85 (CH=), 58.85 (C), 57.91 (CH), 52.92 ($OCH_3$), 48.56 (CH), 42.42 (C), 34.44 ($CH_2$), 33.48 (CH), 32.73 ($CH_2$), 26.72 ($CH_3$), 25.12 ($CH_2$), 23.26, 21.72 (2 x $CH_3$); FT-IR 1726, 1741 (C=O, ester), 1710 (C=O, ketone) $cm^{-1}$; HRMS $M^+$ 262.1561 (calcd. for $C_{16}H_{22}O_3$: 262.1570). Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73.24; H, 8.46; found: C, 73.54; H, 8.61.

### 3-Carbomethoxy-4-ethyl-6,6-dimethylbicyclo[3.1.1]hept-2-one (88) and 3-Carbomethoxy-4-(4-chloro-2-methyl-2-butenyl)-6,6-dimethylbicyclo[3.1.1]hept-2-one (89)



**88**

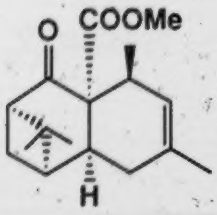


**89**

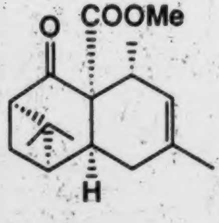
Enone ester **27** (90.9 mg, 0.468 mmol) was dissolved in 3.4 ml of ether and cooled to -20°C. Then 0.26 ml of diethylaluminium chloride (1.8 *M* solution) and isoprene (0.94 ml, 9.37 mmol) were added under an atmosphere of argon. After stirring for 3 h, 3.0 ml of saturated aqueous sodium bicarbonate was added. The reaction mixture was extracted with ether. The ether extracts were washed with water, dried, filtered and concentrated. Flash chromatography of the residue using 1-5% ether in petroleum ether as the eluant gave an inseparable mixture of **85** and **88** (47 mg) in a ratio of 1 : 5 (from $^1$H NMR integration), respectively. The following is the spectroscopic data for **88**: $^1$H NMR (300 MHz, $CDCl_3$) δ 3.81 (s, 3H, $OCH_3$), 3.24 (d, 1H, $C\mathbf{H}COOCH_3$, $J$ = 8 Hz), 2.64 (dd, 1H, O=CC**H**, $J$ = 5, 5 Hz), 2.45 (m, 2H, CHC**H**H, C**H**Et), 2.16 (m, 1H, $C(CH_3)_2C\mathbf{H}$), 1.64 (d, 1H, CHCH**H**, $J$ = 11 Hz), 1.48 (m, 2H, $C\mathbf{H}_2CH_3$), 1.36 (s, 3H, *exo* $CH_3$), 0.97 (s, 3H, *endo* $CH_3$), 0.92 (t, 3H, $CH_2C\mathbf{H}_3$, $J$ = 7.5 Hz); FT-IR 1744 (C=O, ester), 1712 (C=O, ketone) cm$^{-1}$; HRMS M$^+$ 224.1412 (calcd. for $C_{13}H_{20}O_3$: 224.1413). Further elution gave a mixture of unidentified compounds (8.2 mg) and **89** (9.3 mg, 0.031 mmol, 7% yield) as an oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 5.48 (tq, 1H, $CH_3C{=}C\mathbf{H}$, $J$ = 7.5, 1 Hz), 4.04, 4.05 (both d, each 1H, $C\mathbf{H}_2Cl$, $J$ = 7.5 Hz each), 3.77 (s, 3H, $OC\mathbf{H}_3$), 3.24 (d, 1H, $C\mathbf{H}COOCH_3$, $J$ = 8 Hz), 2.80 (m, 1H, $C\mathbf{H}CHCOOCH_3$), 2.65 (dd, 1H, O=CC**H**, *J* = 5, 5 Hz), 2.46 (m, 1H, CHCH**H**), 2.16 (d, 2H, C**H**$_2$C=, *J* = 7.5 Hz), 2.09 (m, 1H, C(CH$_3$)$_2$C**H**), 1.72 (d, 3H, C**H**$_3$C=CH, *J* = 1 Hz), 1.65 (d, 1H, CHCH**H**, *J* = 11 Hz), 1.36 (s, 3H, *exo* CH$_3$), 0.96 (s, 3H, *endo* CH$_3$); $^{13}$C APT NMR (75 MHz, CDCl$_3$) δ 207.73 (p), 170.59 (p), 139.44 (p), 123.70 (a), 57.48 (a), 57.18 (a), 52.40 (a), 44.82 (p, a), 43.42 (p), 40.42 (p), 34.01 (a), 26.71 (a), 23.05 (p), 21.21 (a), 15.95 (a); FT-IR 1740 (C=O, ester), 1711 (C=O, ketone) cm$^{-1}$; HRMS M$^+$ 298.1344, 300.1306 (calcd. for $C_{16}H_{23}O_3Cl$: 298.1336, 300.1306).

### ZnCl$_2$ catalyzed reactions

**(1R, 3R, 4S, 8S, 9R)- (90) and (1R, 3R, 4R, 8S, 9R)-(+)-3-Carbomethoxy-4,6,10,10-tetramethyltricyclo[7.1.1.0$^{3,8}$]undec-5-en-2-one (91)**



**90**



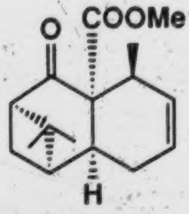
**91**

Enone ester **27** (97.3 mg, 0.501 mmol) was dissolved in ether (1.23 ml) and cooled to -20°C. To this was added ZnCl$_2$ solution (68.3 mg, 0.501 mmol in 2.42 ml ether) and *trans*-2-methyl-1,3-pentadiene (0.57 ml, 5.01 mmol) under an atmosphere of argon. The mixture was stirred for 24 h and 3 ml of saturated aqueous sodium bicarbonate solution was added. The mixture was then extracted with ether and the ether extracts were washed with water, dried, filtered and concentrated. Flash chromatography of the residue on silica gel using 2-5% ether in petroleum ether as the eluant gave impure **90**. Further elution with 5% ether in petroleum ether gave pure **91** (126.1 mg, 0.459 mmol, 91% yield) as a colorless oil: $[\alpha]_D^{23}$ = +27.4° (c. 1.05, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.19 (m, 1H, =C**H**), 3.69 (s, 3H, OC**H**$_3$), 2.94 (dddd, 1H, CHC**H**, $J$ = 7.5, 7.5, 2, 2 Hz), 2.66 (dd, 1H, O=CC**H**, $J$ = 5.5, 5.5 Hz), 2.46 (m, 2H, CHC**H**$_{exo}$H, =CHCH**H**), 2.27 (dd, 1H, C**H**HC=, $J$ = 16, 8 Hz), 2.09 (ddd, 1H, C(CH$_3$)$_2$C**H**, $J$ = 5.5, 5.5, 2 Hz), 1.91 (m, 1H, CH**H**C=), 1.82 (d, 1H, CHCH**H**$_{endo}$, $J$ = 11 Hz), 1.76 (br s, 3H, =CC**H**$_3$), 1.32 (s, 3H, *exo* C**H**$_3$), 1.26 (d, 3H, CHC**H**$_3$, $J$ = 7 Hz), 0.90 (s, 3H, *endo* C**H**$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 208.54 (C=O), 171.95 (OC=O), 135.15 (C=), 125.55 (CH=), 60.62 (C), 58.43 (CH), 51.85 (OCH$_3$), 48.95 (CH), 41.43 (C), 38.69, 36.65 (2 x CH), 33.57 (CH$_2$), 26.50 (CH$_3$), 24.92 (CH$_2$), 23.01, 21.61, 17.57 (3 x CH$_3$); FT-IR 1746 (C=O, ester), 1711 (C=O, ketone) cm$^{-1}$; HRMS M$^+$ 276.1723 (calcd. for $C_{17}H_{24}O_3$: 276.1726). Anal. Calcd. for $C_{17}H_{24}O_3$: C, 73.87; H, 8.76; found: C, 73.80; H, 8.71. Flash chromatography again of the impure **90** with 2-4% ether in petroleum ether gave **90** (12.5 mg, 0.045 mmol, 9%) as a colorless oil: $[\alpha]_D^{23}$ = +145.34° (c. 0.869, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.42 (m, 1H, =C**H**), 3.76 (s, 3H, OC**H**$_3$), 3.25 (dddd, 1H, CHC**H**, $J$ = 6, 6, 1.5, 1.5 Hz), 3.16 (m, 1H, =CHC**H**$_e$H), 2.55 (dd, 1H, O=CC**H**, $J$ = 5.5, 5.5 Hz), 2.44 (dddd, 1H, CHC**H**$_{exo}$H, $J$ = 11, 5.5, 5.5, 1.5 Hz), 2.15 (m, 1H, C**H**$_e$HC=), 1.96 (m, 2H, C(CH$_3$)$_2$C**H**, CH**H**$_{ax}$C=), 1.87 (d, 1H, CHCH**H**$_{endo}$, $J$ = 11 Hz), 1.77 (br s, 3H, =CC**H**$_3$), 1.32 (s, 3H, *exo* C**H**$_3$), 1.04 (d, 3H, CHC**H**$_3$, $J$ = 7.5 Hz), 0.89

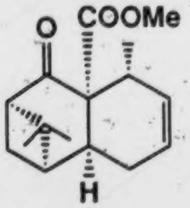
(s, 3H, *endo* $CH_3$); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 209.81 (C=O), 174.04 (OC=O), 135.06 (=C), 125.92 (=CH), 61.39 (C), 58.50 (CH), 53.02 ($OCH_3$), 47.63 (CH), 42.57 (C), 37.02 (CH), 35.68 (CH), 33.31 ($CH_2$), 26.66 ($CH_3$), 24.91 ($CH_2$), 23.88, 21.60, 18.41 (3 x $CH_3$); FT-IR 1724 (C=O, ester), 1708 (C=O, ketone) $cm^{-1}$; HRMS $M^+$ 276.1719 (calcd. for $C_{17}H_{24}O_3$: 276.1726).

The adducts **92-98** showed the following spectral data.

### (1R, 3R, 4S, 8S, 9R)- (92) and (1R, 3R, 4R, 8S, 9R)-(+)-3-Carbomethoxy-4,10,10-trimethyltricyclo[7.1.1.0$^{3,8}$]undec-5-en-2-one (93)



**92**



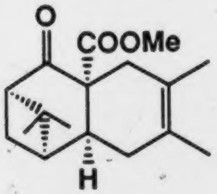
**93**

**92** (a colorless oil): $[\alpha]_D^{23}$ = +153° (c. 1.66, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.97 (dddd, 1H, CHHC**H**=, $J$ = 10, 5, 5, 1.5 Hz), 5.80 (dddd, 1H, CH=C**H**, $J$ = 10, 5, 1.5, 1.5 Hz), 3.77 (s, 3H, OC**H**$_3$), 3.25 (dddd, 1H, CHC**H**, $J$ = 6.5, 6.5, 1.5, 1.5 Hz), 3.22 (m, 1H, C**H**$CH_3$), 2.58 (dd, 1H, O=CC**H**, $J$ = 5.5, 5.5 Hz), 2.48 (dddd, 1H, CHC**H**$_{exo}$H, $J$ = 11, 6, 6, 1.5 Hz), 2.21 (m, 1H, C**H**$_e$HC=), 2.01 (m, 2H, $C(CH_3)_2$C**H**, CH**H**$_{ax}$C=), 1.86 (d, 1H, CHCH**H**$_{endo}$, $J$ = 11 Hz), 1.33 (s, 3H, *exo* C**H**$_3$), 1.06 (d, 3H, CHC**H**$_3$, $J$ = 7.5 Hz), 0.90 (s, 3H, *endo* C**H**$_3$); $^{13}C$ APT NMR (75 MHz,

$CDCl_3$) δ 209.76 (C=O), 173.96 (OC=O), 133.07, 127.01 (CH=CH), 61.80 (C), 58.38 (CH), 53.08 ($OCH_3$), 47.63 (CH), 42.40 (C), 36.46, 35.20 (2 x CH), 27.82 ($CH_2$), 26.66 ($CH_3$), 25.21 ($CH_2$), 21.65, 18.16 (2 x $CH_3$); FT-IR 1724 (C=O, ester), 1710 (C=O, ketone) $cm^{-1}$; HRMS $M^+$ 262.1569 (calcd. for $C_{16}H_{22}O_3$: 262.1570).

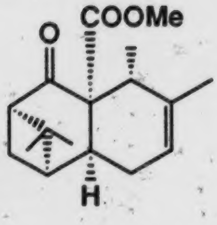
**93** (a colorless oil): $[\alpha]_D^{23}$ = +44.9° (c. 1.50, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 5.92 (ddd, 1H, CHHC**H**=, *J* = 9.5, 6, 3 Hz), 5.56 (ddd, 1H, CH=C**H**, *J* = 9.5, 3, 3 Hz), 3.72 (s, 3H, OC**H**$_3$), 2.90 (dddd, 1H, CHC**H**, *J* = 7.5, 7.5, 1.5, 1.5 Hz), 2.62 (dd, 1H, O=CC**H**, *J* = 5.5, 5.5 Hz), 2.46 (m, 3H, C**H**$CH_3$, CHC**H**$_{exo}$H, C**H**$_e$HC=), 2.11 (ddd, 1H, $C(CH_3)_2$C**H**, *J* = 6, 6, 2 Hz), 1.92 (m, 1H, CH**H**$_{ax}$C=), 1.86 (d, 1H, CHCH**H**$_{endo}$, *J* = 11 Hz), 1.34 (s, 3H, *exo* C**H**$_3$), 1.30 (d, 3H, CHC**H**$_3$, *J* = 7 Hz), 0.94 (s, 3H, *endo* C**H**$_3$); $^{13}C$ APT NMR (75 MHz, $CDCl_3$) δ 208.36 (C=O), 171.89 (OC=O), 132.49, 126.90 (CH=CH), 60.78 (C), 58.25 (CH), 51.77 ($OCH_3$), 48.94 (CH), 41.53 (C), 37.80 (CH), 36.21 (CH), 28.17 ($CH_2$), 26.46 ($CH_3$), 24.86 ($CH_2$), 21.51, 17.25 (2 x $CH_3$); FT-IR 1744, 1722 (C=O, ester), 1709 (C=O, ketone) $cm^{-1}$; HRMS $M^+$ 262.1568 (calcd. for $C_{16}H_{22}O_3$: 262.1570). Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73.24; H, 8.46; found: C, 73.02; H, 8.43.

### (1R, 3R, 8S, 9R)-(+)-3-Carbomethoxy-5,6,10,10-tetramethyltricyclo[7.1.1.$0^{3,8}$]undec-5-en-2-one (94)

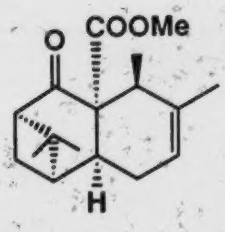


**94** (a colorless oil purified by gravity chromatography on neutral alumina): $[\alpha]_D^{23}$ = +68.97° (c. 1.07, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H, OC**H**$_3$), 3.18 (dddd, 1H, CHC**H**, *J* = 9, 7.5, 1.5, 1.5 Hz), 2.87 (d, 1H, =CC**H**$_e$H, *J* = 14.5 Hz), 2.66 (dd, 1H, O=CC**H**, *J* = 5.5, 5.5 Hz), 2.47 (m, 1H, CHC**H**$_{exo}$H), 2.27 (br d, 1H, =CCH**H**$_{ax}$, *J* = 14.5 Hz), 2.11 (m, 2H, C($CH_3$)$_2$C**H**, C**H**$_e$HC=), 1.93 (m, 2H, CHCH**H**$_{endo}$, CH**H**$_{ax}$C=), 1.68 (br s, 3H, =CC**H**$_3$), 1.65 (br s, 3H, =CC**H**$_3$), 1.34 (s, 3H, *exo* $CH_3$), 0.96 (s, 3H, *endo* $CH_3$); $^{13}C$ APT NMR (75 MHz, $CDCl_3$) δ 210.07 (C=O), 172.25 (OC=O), 128.19, 125.62 (C=C), 60.20 (C), 57.98 (CH), 52.68 ($OCH_3$), 48.06 (CH), 42.00 (C), 40.99 ($CH_2$), 34.57 ($CH_2$), 33.75 (CH), 26.69 ($CH_3$), 24.90 ($CH_2$), 21.75, 18.95, 18.43 (3 x $CH_3$); FT-IR 1727 (C=O, ester), 1710 (C=O, ketone) $cm^{-1}$; HRMS $M^+$ 276.1725 (calcd. for $C_{17}H_{24}O_3$: 276.1726). Anal. Calcd. for $C_{17}H_{24}O_3$: C, 73.87; H, 8.76; found: C, 73.92; H, 8.77.

**(1R, 3R, 4R, 8S, 9R)- (95) and (1R, 3R, 4S, 8S, 9R)-(+)-3-Carbomethoxy-4,5,10,10-tetramethyltricyclo[7.1.1.0$^{3,8}$]undec-5-en-2-one (96)**



95



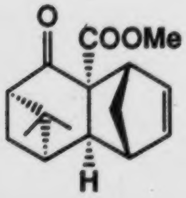
96

Reaction of **27** with 3-methyl-1,3-pentadiene did not go to completion, 24% of **27** was recovered.

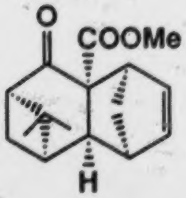
**95** (a white solid): $[\alpha]_D^{23}$ = +99.65° (c. 2.56, $CHCl_3$); mp 66-68°C; $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.60 (m, 1H, C**H**=), 3.72 (s, 3H, $OCH_3$), 3.06 (dddd, 1H, CHC**H**, *J* = 8, 6, 1.5, 1.5 Hz), 2.73 (br q, 1H, C**H**$CH_3$, *J* = 7 Hz), 2.64 (dd, 1H, O=CC**H**, *J* = 5.5, 5.5 Hz), 2.43 (m, 2H, CHC**H**$_{exo}$H, C**H**$_e$HC=), 2.10 (ddd, 1H, $C(CH_3)_2$C**H**, *J* = 6, 6, 2 Hz), 1.97 (d, 1H, CHCH**H**$_{endo}$, *J* = 11 Hz), 1.87 (m, 1H, CH**H**$_{ax}$C=), 1.70 (br s, 3H, =C$CH_3$), 1.33 (s, 3H, *exo* $CH_3$), 1.23 (d, 3H, CHC**H**$_3$, *J* = 7 Hz), 0.93 (s, 3H, *endo* $CH_3$); $^{13}C$ APT NMR (75 MHz, $CDCl_3$) δ 208.74 (C=O), 172.00 (OC=O), 138.76 (C=), 122.10 (CH=), 63.12 (C), 58.32 (CH), 52.03 ($OCH_3$), 49.30 (CH), 42.46 (C), 41.06, 35.72 (2 x CH), 28.11 ($CH_2$), 26.66 ($CH_3$), 24.51 ($CH_2$), 21.67, 20.24, 13.95 (3 x $CH_3$); FT-IR 1723 (C=O, ester), 1702 (C=O, ketone) $cm^{-1}$; HRMS $M^+$ 276.1727 (calcd. for $C_{17}H_{24}O_3$: 276.1726). Anal. Calcd. for $C_{17}H_{24}O_3$: C, 73.87; H, 8.76; found: C, 73.83; H, 8.88.

**96** (an oil): $[\alpha]_D^{23}$ = +84.58° (c. 2.32, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.64 (br d, 1H, C**H**=, *J* = 7.5 Hz), 3.71 (s, 3H, $OCH_3$), 3.28 (dddd, 1H, CHC**H**, *J* = 11, 7.5, 2, 2 Hz), 3.04 (q, 1H, C**H**$CH_3$, *J* = 7.5 Hz), 2.65 (dd, 1H, O=CC**H**, *J* = 5.5, 5.5 Hz), 2.51 (dddd, 1H, CHC**H**$_{exo}$H, *J* = 11, 6, 6, 2 Hz), 2.18 (ddd, 1H, C**H**$_e$HC=, *J* = 15, 7, 7 Hz), 2.03 (ddd, 1H, C($CH_3$)$_2$C**H**, *J* = 6, 6, 2.5 Hz), 1.88 (m, 1H, CH**H**$_{ax}$C=), 1.77 (d, 1H, CHCH**H**$_{endo}$, *J* = 11 Hz), 1.68 (dd, 3H, =CC**H**$_3$, *J* = 2.5, 1.5 Hz), 1.34 (s, 3H, *exo* C**H**$_3$), 1.00 (d, 3H, CHC**H**$_3$, *J* = 7.5 Hz), 0.82 (s, 3H, *endo* C**H**$_3$); $^{13}$C APT NMR (75 MHz, $CDCl_3$) δ 209.45 (C=O), 173.47 (OC=O), 139.79 (C=), 121.44 (CH=), 61.59 (C), 58.87 (CH), 53.15 ($OCH_3$), 46.00, 44.05 (2 x CH), 40.27 (C), 36.27 (CH), 27.41 ($CH_2$), 26.73 ($CH_3$), 24.47 ($CH_2$), 22.25, 22.05, 16.50 (3 x $CH_3$); FT-IR 1742 (C=O, ester), 1713 (C=O, ketone) cm$^{-1}$; HRMS M$^+$ 276.1727 (calcd. for $C_{17}H_{24}O_3$: 276.1726).

**(1R, 3R, 4S, 7R, 8S, 9R)- (97) and (1R, 3R, 4R, 7S, 8S, 9R)-3-Carbomethoxy-10,10-dimethyltetracyclo[7.1.1.1.$^{4,7}$0$^{3,8}$]dodec-5-en-2-one (98)**



**97**



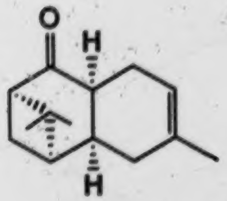
**98**

After the reaction was completed, flash chromatography of the residue on silica gel with 4% ether in petroleum ether gave a mixture of impure **97** and **98**. Bulb to bulb distillation (64°C/1-1.5 mm Hg) gave a mixture of pure **97** and **98** (in the ratio of 89 : 11 respectively): FT-IR 1731 (C=O, ester), 1709 (C=O, ketone) cm$^{-1}$; HRMS M$^+$ 260.1415 (calcd. for $C_{16}H_{20}O_3$: 260.1413). $^1$H NMR (300 MHz, $CDCl_3$) showed two sets of signals; the major set for

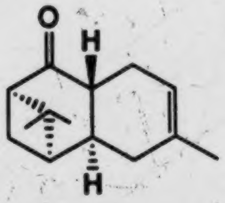
**97**: δ 6.46 (dd, 1H, C**H**=CH, *J* = 5.5, 3 Hz), 5.98 (dd, 1H, CH=C**H**, *J* = 5.5, 3 Hz), 3.67 (s, 3H, O$\mathrm{CH_3}$), 3.50 (sharp m, 1H, =CHC**H**), 2.76 (sharp m, 1H, C**H**CH=), 2.70 (dd, 1H, O=CC**H**, *J* = 6, 6 Hz), 2.63 (m, 1H, CHC$\mathbf{H}_{exo}$H), 2.61 (sharp m, 1H, CHC**H**), 2.42 (m, 1H, $\mathrm{C(CH_3)_2C}$**H**), 2.02 (d, 1H, CHCH$\mathbf{H}_{endo}$, *J* = 12 Hz), 1.98 (br d, 1H, CHC**H**HCH, *J* = 10.5 Hz), 1.40 (s, 3H, *exo* $\mathrm{CH_3}$), 1.34 (m, 1H, CHCH**H**CH), 0.92 (s, 3H, *endo* $\mathrm{CH_3}$); the minor set for **98**: 6.30 (dd, 1H, CH=C**H**, *J* = 5.5, 3 Hz), 6.13 (dd, 1H, C**H**=CH, *J* = 5.5, 3 Hz), 3.76 (s, 3H, O$\mathrm{CH_3}$), 3.37 (m, 1H), 3.31 (m, 1H), 2.97 (m, 1H), 2.28 (m, 2H), 2.17 (m, 1H), 1.33 (s, 3H, *exo* $\mathrm{CH_3}$), 0.92 (s, 3H, *endo* $\mathrm{CH_3}$).

## II. CYCLOBUTANE RING FRAGMENTION REACTIONS

### (1R, 3S, 8S, 9R)-(+)- (105) and (1R, 3R, 8S, 9R)-(-)-6,10,10-Trimethyltricyclo[7.1.1.0$^{3,8}$]undec-5-en-2-one (106)



**105**



**106**

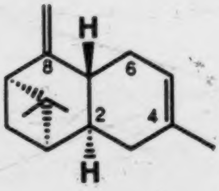
Keto ester **85** (4.632 g, 17.7 mmol) was dissolved in 30 ml of 2,4,6-collidine under an atmosphere of argon. Anhydrous lithium iodide(18,94 g, 142 mmol) and then water (2.54 ml, 0.142 mol) were introduced to the stirred solution. The mixture was heated under reflux for 2.3 h, cooled to room temperature, poured into cold 5% hydrochloric acid and extracted with ether. The extracts were washed with ice-cold 5% hydrochloric acid and water, dried, filtered and concentrated. The residue was subjected to flash chromatography on silica gel with 4% ether in petroleum ether as eluant afforded **105** (0.222 g, 1.1 mmol, 6% yield): $[\alpha]_D^{23}$ = +107.3° (c. 2.07, CHCl$_3$); mp 52-54 °C; $^1$H NMR (300 MHz, CDCl$_3$) δ 5.67 (dm, 1H, =C**H**, *J* = 6 Hz), 2.63 (dd, 1H, =CHC**H**H, *J* = 14, 7 Hz), 2.58 (dd, 1H, O=CC**H**, *J* = 5.5, 5.5 Hz), 2.47 (m, 1H, C**H**$_{exo}$HCH), 2.34 (m, 2H, C**H**C=O, CHC**H**); 2.06 (ddd, 1H, C(CH$_3$)$_2$C**H**, *J* = 5.5, 5.5, 2 Hz), 1.99 (dd, 1H, C**H**HC=, *J* = 15, 6 Hz), 1.93 (m, 1H, CH**H**C=), 1.82 (m, 1H, =CHCH**H**), 1.78 (br s, 3H, =CC**H**$_3$), 1.65 (d, 1H, CH**H**$_{endo}$CH, *J* = 11 Hz), 1.34 (s, 3H, *exo* C**H**$_3$), 0.91 (s, 3H, *endo* C**H**$_3$); $^{13}$C APT NMR (75 MHz, CDCl$_3$) δ 216.31 (C=O), 137.75 (=C), 121.40 (=CH), 57.51, 47.74, 44.21 (3 x CH), 40.38 (C), 32.95 (CH$_2$), 32.05 (CH), 29.00 (CH$_2$), 25.85 (CH$_3$), 23.62 (CH$_2$), 23.17, 21.82 (2 x CH$_3$); FT-IR 1705 (C=O) cm$^{-1}$; HRMS M$^+$ 204.1512 (calcd. for $C_{14}H_{20}O$: 204.1514). Continued elution gave a mixture of **105** and **106** (0.393 g, 1.9 mmol, 11% yield in the ratio of 1 : 2 from $^1$H NMR integration). Further elution gave pure **106** (2.899 g, 14.2 mmol, 80% yield): $[\alpha]_D^{23}$ = -47.8° (c. 2.286, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$) δ 5.48 (br s, 1H, =C**H**), 2.60 (dd, 1H, O=CC**H**, *J* = 5, 5 Hz), 2.30-2.50 (m, 3H), 1.83-2.22 (m, 6H), 1.70 (br s, 3H, =CC**H**$_3$), 1.38 (s, 3H, *exo* C**H**$_3$), 0.78 (s, 3H, *endo* C**H**$_3$); $^{13}$C APT NMR (75 MHz, CDCl$_3$) δ 214.74 (C=O), 135.39 (=C), 121.16 (=CH), 58.53, 46.36, 44.99 (3 x CH), 44.74 (C), 36.56 (CH$_2$), 36.50 (CH), 26.77 (CH$_3$), 24.99, 24.03 (2 x CH$_2$), 23.70, 21.93 (2 x CH$_3$); FT-IR 1714

(C=O) $cm^{-1}$; HRMS $M^+$ 204.1516 (calcd. for $C_{14}H_{20}O$: 204.1514). Anal. Calcd. for $C_{14}H_{20}O$: C, 82.29; H, 9.87; found: C, 82.59; H, 9.78.

### Epimerization of **105**

Ketone **105** (21 mg, 0.103 mmol) was dissolved in 5 ml of methanol and 1 ml of 3 *M* aqueous sodium hydroxide solution was then added. After refluxing for 24 h, water was added and the mixture was extracted with ether. The extracts were washed with saturated aqueous sodium chloride solution, dried, filtered and concentrated. The crude product (19.4 mg) was a mixture of **105** and **106** in the ratio of 1 : 9 respectively (from $^1H$ nmr 300 MHz integration).

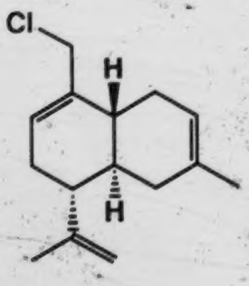
### **(1R, 2S, 7R, 9R)-(-)-4,10,10-Trimethyl-8-methylenetricyclo-[7.1.1.0$^{2,7}$]undec-4-ene (107)**



Potassium hydride (1.44 g, 35% by wt) in a 3-necked flask was washed with benzene (dried) three times under argon atmosphere. DMSO (6 ml) was introduced *via* a syringe and the mixture was stirred at room temperature until the evolution of hydrogen was no longer observed (*ca.* 25 min). Methyltriphenylphosphonium bromide (4.30 g, 0.012 mol) in 11 ml of DMSO was then added to the light greenish yellow solution. The resulting bright yellowish green solution was stirred at room temperature for 10 min before use.

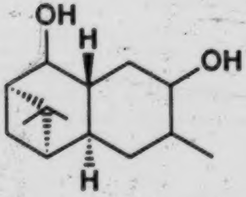
Ketone **106** (1.176 g, 5.77 mmol) in 4 ml of benzene was added to the above solution of methylenetriphenylphosphorane. The resulting dark red solution was stirred at room temperature for 20 h, water was then added. The mixture was extracted with petroleum ether. The combined extracts were washed with water, dried, filtered and concentrated. The crude product was then passed through a layer of silica gel in a sintered funnel and the silica gel was washed with 1-2% ether in petroleum ether. The filtrate was concentrated to give **107** (1.1585 g, 5.74 mmol, 99% yield) as a colorless liquid: $[\alpha]_D^{23}$ = -84.67° (c. 2.10, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 5.47 (br m, 1H, =C**H**), 4.66 (dd, 1H, =CH**H**, $J$ = 2, 2 Hz), 4.60 (dd, 1H, =CH**H**, $J$ = 2, 2 Hz), 2.53 (dd, 1H, $CH_2$=CC**H**, $J$ = 5.5, 5.5 Hz), 2.18-2.40 (m, 3H), 1.98 (m, 2H), 1.79 (m, 3H), 1.70 (m, 4H, CHC$H\mathbf{H}_{endo}$, =C$\mathbf{H}_3$), 1.29 (s, 3H, *exo* C$\mathbf{H}_3$), 0.66 (s, 3H, *endo* C$\mathbf{H}_3$); $^{13}C$ APT NMR (75 MHz, $CDCl_3$) $\delta$ 153.74, 135.65 (2 x =C), 121.50 (=CH), 103.85 (=$CH_2$), 52.90, 45.41 (2 x CH), 42.85 (C), 38.24, 37.46 (2 x CH), 37.27, 28.37 (2 x $CH_2$), 26.80 ($CH_3$), 24.18 ($CH_2$), 23.81, 21.39 (2 x $CH_3$); FT-IR 1643 (C=C) $cm^{-1}$; HRMS $M^+$ 202.1722 (calcd. for $C_{15}H_{22}$: 202.1723).

### (1R, 5R, 6S)-(-)-2-Chloromethyl-8-methyl-5-(1-methylethenyl)-bicyclo[4.4.0]dec-2,8-diene (108)



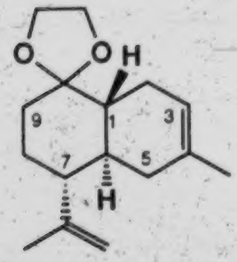
Phenyl dichlorophosphate (73 µl, 0.491 mmol) and DMSO (63 µl, 0.892 mmol) were added to 0.5 ml of dichloromethane (dried) at -40°C. A colorless solution formed. Compound **107** (90.1 mg, 0.446 mmol in 1 ml of dichloromethane) was then added. After stirring at -40°C for 1 h and at -20°C to 10°C for 45 min, 50 µl of water was added. The mixture was filtered through a layer of silica gel in a sintered funnel and washed with 40% ether in petroleum ether. The filtrate was concentrated and the residue was distilled (bulb to bulb, at 66-68°C/1.5-2 mm Hg) to give **108** (58.8 mg, 0.248 mmol, 56% yield): $[\alpha]_D^{26}$ = -193.9° (c. 2.33, $CHCl_3$); mp 40-41°C; $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.86 (br d, 1H, $CH_2ClC{=}C\mathbf{H}$, $J$ = 5 Hz), 5.49 (br d, 1H, $CH_3C{=}C\mathbf{H}$, $J$ = 5 Hz), 4.78 (m, 2H, $CH_3C{=}C\mathbf{H_2}$), 4.20 (dm, 1H, $C\mathbf{H}HCl$, $J$ = 11 Hz), 3.95 (d, 1H, $CH\mathbf{H}Cl$, $J$ = 11 Hz), 1.50-2.50 (m, 9H), 1.67 (br s, 6H, $\mathbf{CH_3}C{=}CH_2$, $\mathbf{CH_3}C{=}CH$); $^{13}C$ APT NMR (75 MHz, $CDCl_3$) δ 146.88, 136.36, 134.42 (3 x =C), 127.85, 120.20 (2 x =CH), 112.25 (=$CH_2$), 47.92 ($CH_2Cl$), 47.50, 38.17, 37.33 (3 x CH), 35.61, 31.00, 29.80 (3 x $CH_2$), 23.50, 18.21 (2 x $CH_3$); FT-IR 1643 (C=C) $cm^{-1}$; HRMS $M^+$ 238.1305, 236.1331 (calcd. for $C_{15}H_{21}Cl$: 238.1303, 236.1333).

### 6,10,10-Trimethyltricyclo[7.1.1.0$^{3,8}$]undec-2,5-diols (110)

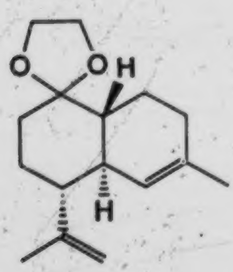


To a solution of **106** (119.7 mg, 0.587 mmol) in THF (0.60 ml) cooled to 0°C, was added dropwise 1.50 ml of 1 *M* $BH_3$-THF solution under an atmosphere of argon. The reaction mixture was stirred at 0°C for 1 h and for a further 2 h at room temperature . Excess borane was decomposed by the dropwise addition of 0.6 ml of water. A 0.6 ml of 3 *M* aqueous sodium hydroxide solution was introduced, followed by dropwise addition of 0.6 ml 30% hydrogen peroxide solution. The reaction mixture was stirred for 1 h at room temperature and potassium carbonate (1.25 g) was then added. The mixture was extracted with ether (3 x 5 ml) and the combined organic layers were washed with water, dried, filtered and concentrated to give **110** (177.5 mg as a mixture of 1 : 2): $^1H$ NMR (300 MHz, $CDCl_3$) δ 4.21 (m, 0.67H), 3.92 (m, 0.33H), 3.65 (t, 0.67H, $J = 6.5$ Hz), 3.31 (m, 0.33H), 0.9-2.26 (m, total 22H); FT-IR 3362 (OH) $cm^{-1}$; HRMS $M^+$-$H_2O$ 206.1669 (calcd. for $C_{14}H_{22}O$: 206.1672); $M^+$-$2H_2O$ 188.1562 (calcd. for $C_{14}H_{20}$: 188.1566).

**(1R, 6S, 7R)-10,10-Ethylenedioxy-4-methyl-7-(1-methylethenyl)-bicyclo[4.4.0]dec-3-ene (111) and (1R, 6S, 7R)-10,10-ethylenedioxy-4-methyl-7-(1-methylethenyl)bicyclo[4.4.0]dec-4-ene (112)**



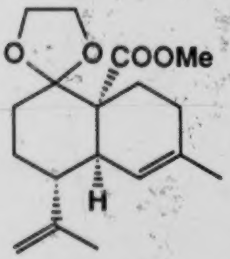
**111**



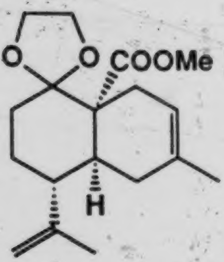
**112**

Ethylene glycol (43.1 mg, 0.69 mmol) and *p*-toluenesulfonic acid (13.9 mg, 0.073 mmol) were added to a solution of **106** (65.2 mg, 0.32 mmol) in 8 ml of benzene. The mixture was heated under reflux with removal of water by a Dean-Stark apparatus for 20 h. The benzene layer was washed twice with 1 *M* aqueous sodium hydroxide solution, saturated aqueous sodium chloride solution, dried, filtered and concentrated. Flash chromatography of the residue with 4% ether in petroleum ether gave a mixture of **111** and **112** (64.0 mg, 81% yield) in the ratio of 2 : 1, respectively: $^1$H NMR (300 MHz, $CDCl_3$) δ 5.27 (br s, 0.67H, =C**H**), 5.15 (q, 0.33H, CHC**H**=, *J* = 1.5 Hz), 4.81 (m, 0.33H, C=CH**H**), 4.65 (m, 1.67H, C=CH**H**), 3.95 (m, total 4H, $OCH_2CH_2O$), 1.30-2.15 (m, total 17H); FT-IR 1644 (C=C) cm$^{-1}$; HRMS M$^+$ 248.1774 (calcd. for $C_{16}H_{24}O_2$: 248.1777).

**(1R, 6S, 7R)-1-Carbomethoxy-10,10-ethylenedioxy-4-methyl-7-(1-methylethenyl)bicyclo[4.4.0]dec-4-ene (113) and (1R, 6S, 7R)-1-carbomethoxy-10,10-ethylenedioxy-4-methyl-7-(1-methylethenyl)bicyclo[4.4.0]dec-3-ene (114)**



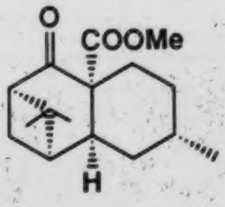
**113**



**114**

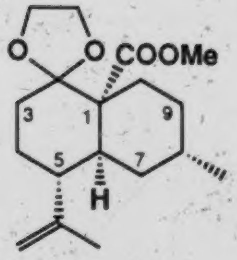
To a solution of keto ester **85** (88.6 mg, 0.338 mmol) was introduced 50.5 mg (0.813 mmol) of ethylene glycol and 16.6 mg (0.086 mmol) of *p*-toluenesulfonic acid. The reaction mixture was refluxed with removal of water by a Dean-Stark apparatus for 48 h. The benzene layer was washed with 1 *M* aqueous sodium hydroxide solution, saturated aqueous sodium chloride solution, dried, filtered and concentrated. Flash chromatography with 6-20% ether in petroleum ether recovered 48.0 mg of starting material **85**. Continuing elution gave a mixture of **113** and **114** (41.9 mg, 92% yield based on consumed starting material) in the ratio of 41 : 59, respectively: $^1$H NMR (300 MHz, $CDCl_3$) δ 5.37 (dq, 0.5H, $CH{=}CCH_3$, $J$ = 5, 1.5 Hz), 5.30, (br s, 0.5H, $CH_3C{=}CH$), 4.75 (m, 2H, $C{=}CH_2$), 3.79-4.0 (m, 4H, $OCH_2CH_2O$), 3.70, 3.67 (both s, 3H, $OCH_3$), 2.90, 2.84 (both m, 1H), 2.22-2.50 (m, 2H), 1.46-2.16 (m, 13H); FT-IR 1729 (C=O, ester), 1643 (C=C) cm$^{-1}$; HRMS M$^+$ 306.1830 (calcd. for $C_{18}H_{26}O_4$: 306.1832).

### (1R, 3R, 6S, 8S, 9R)-(+)-3-Carbomethoxy-6,10,10-trimethyltricyclo[7.1.1.0$^{3,8}$]undec-2-one (115)



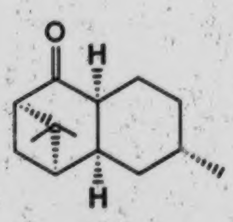
Keto ester **85** (48 mg, 0.183 mmol) in a solution of ethanol (10 ml), containing 0.5 ml of glacial acetic acid and 12 mg of $PtO_2$ was hydrogenated at 35 psi for 24 h. The reaction mixture was then filtered through a layer of celite in a sintered funnel and concentrated. Flash chromatography of the residue with 5% ether in petroleum ether gave compound **115** in quantitative yield: $[\alpha]_D^{26}$ = +122.62° (c. 1.70, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.80 (s, 3H, $OC\mathbf{H}_3$), 3.02 (br d, 1H, CHC**H**, $J$ = 7 Hz), 2.62 (dd, 1H, O=CC**H**, $J$ = 5.5, 5.5 Hz), 2.56 (m, 2H, CHC**H**$_{exo}$H, $CH_2$CH**H**), 2.18 (d, 1H, CHCH**H**$_{endo}$, $J$ = 11 Hz), 2.11 (ddd, 1H, $C(CH_3)_2$C**H**, $J$ = 5.5, 5.5, 1 Hz), 1.86 (ddd, 1H, $CH_2$CH**H**, $J$ = 14.5, 13.5, 4.5 Hz), 1.72 (m, 1H, $CHCH_3$CH**H**), 1.60 (m, 2H, $CHCH_3$, C**H**HCH$CH_3$), 1.37 (s, 3H, *exo* $CH_3$), 1.32 (m, 1H, C**H**HCH$CH_3$), 1.01 (m, 4H, *endo* $CH_3$, $CHCH_3$CH**H**), 0.86 (d, 3H, $CHC\mathbf{H}_3$, $J$ = 6.5 Hz); $^{13}C$ APT NMR (75 MHz, $CDCl_3$) $\delta$ 210.33 (p), 172.56 (p), 58.02 (a), 57.44 (p), 52.74 (a), 49.27 (a), 44.92 (p), 38.58 (p), 33.92 (a), 32.59 (p), 31.91 (p), 27.26 (p), 27.07 (a), 26.89 (a), 23.07 (a), 21.62 (a); FT-IR 1737 (C=O, ester), 1707 (C=O, ketone) $cm^{-1}$; HRMS $M^+$ 264.1724 (calcd.for $C_{16}H_{24}O_3$: 264.1726).

**(1R, 5R, 6S, 8S)-1-Carbomethoxy-2,2-ethylenedioxy-8-methyl-5-(1-methylethenyl)bicyclo[4.4.0]decane (117)**

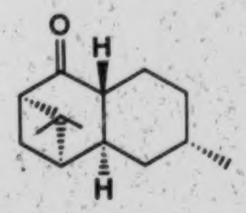


Ethylene glycol (19.6 mg, 0.316 mmol) and *p*-toluenesulfonic acid (6.3 mg, 0.033 mmol) were added to a solution of **115** (27.8 mg, 0.105 mmol) in 8 ml of benzene. The mixture was heated under reflux with removal of water by a Dean-Stark apparatus for 100 h. The benzene layer was washed with 1 *M* aqueous sodium hydroxide solution, saturated sodium chloride solution, dried, filtered and concentrated. Flash chromatography with 3-10% ether in petroleum ether recovered starting material **115** (19.6 mg, 0.074 mmol). Continued elution afforded **117** (6.1 mg, 0.02 mmol, 64% yield based on consumed starting material): $^1$H NMR (300 MHz, $CDCl_3$) δ 4.76 (br s, 1H, C=CHH), 4.73 (m, 1H, C=CH**H**), 3.85 (m, 4H, $OCH_2CH_2O$), 3.73 (s, 3H, $OCH_3$), 2.36 (m, 3H), 1.44-1.78 (m, 11H), 0.80-1.08 (m, 2H), 0.75 (d, 3H, $CHCH_3$, $J = 6.5$ Hz); FT-IR 1728 (C=O) cm$^{-1}$; HRMS M$^+$ 308.1992 (calcd. for $C_{18}H_{28}O_4$: 308.1988).

**(1R, 3S, 6S, 8S, 9R)- (118) and (1R, 3R, 6S, 8S, 9R)-(+)-6,10,10-Trimethyltricyclo[7.1.1.0$^{3,8}$]undec-2-one (119)**



**118**



**119**

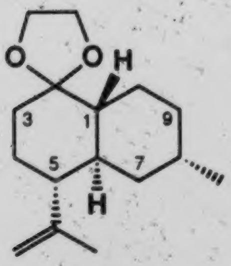
Keto ester **115** (59.2 mg, 0.224 mmol) was dissolved in 1.40 ml of 2,4,6-collidine under an atmosphere of argon. Anhydrous lithium iodide (239.7 mg, 1.8 mmol) and then water (30 µl, 1.8 mmol) were introduced to the stirred solution. The mixture was heated under reflux for 3.5 h, then cooled to room temperature, poured into cold 1 *M* hydrochloric acid and extracted with ether. The extracts were washed with ice-cold 1 *M* hydrochloric acid and water, dried, filtered and concentrated. The residue was subjected to flash chromatography on silica gel eluting with 4% ether in petroleum ether to give **118** (4.0 mg, 0.019 mmol, 8% yield) as a white solid: $[\alpha]_D^{26}$ = +96.13° (c. 0.776, $CHCl_3$); mp 32-33°C; $^1$H NMR (300 MHz, $CDCl_3$) δ 2.55 (dd, 1H, O=CC**H**, *J* = 5, 5 Hz), 2.47 (dddd, 1H, CHC**H**$_{exo}$H, *J* = 10, 8, 6, 1 Hz), 2.37 (m, 2H), 1.99 (m, 4H), 1.66 (m, 2H), 1.42 (m, 1H), 1.34 (s, 3H, *exo* C**H**$_3$), 1.20 (m, 1H), 0.98 (d, 3H, CHC**H**$_3$, *J* = 7 Hz), 0.90 (s, 3H, *endo* C**H**$_3$); $^{13}$C APT NMR (75 MHz, $CDCl_3$) δ 216.68 (p), 58.20 (a), 48.08 (a), 44.94 (a), 41.05 (p), 33.21 (p), 31.20 (p), 28.45 (a), 27.63 (p), 26.04 (a), 25.74 (a), 24.26 (p), 23.20 (a), 21.77 (a); FT-IR 1707 (C=O) cm$^{-1}$; HRMS M$^+$ 206.1665 (calcd. for $C_{14}H_{22}O$: 206.1672). Anal. Calcd. for $C_{14}H_{22}O$: C, 81.49; H, 10.75; found: C, 81.29; H, 10.52. Continued elution gave a mixture of **118** and **119** (8.4 mg, 0.041 mmol, 18% yield) and pure **119** (33.2 mg, 0.161 mmol, 72 % yield): $[\alpha]_D^{26}$ = +66.71° (c. 1.67, $CHCl_3$);

$^1$H NMR (300 MHz, $CDCl_3$) δ 2.54 (dd, 1H, O=CC**H**, *J* = 5, 5 Hz), 2.40 (ddd, 1H, CHC**H**$_{exo}$H, *J* = 10, 7, 5 Hz), 2.17 (m, 2H), 1.93 (m, 3H), 1.85 (d, 1H, CHCH**H**$_{endo}$, *J* = 10 Hz), 1.50-1.72 (m, 3H), 1.42 (m, 2H), 1.36 (s, 3H, *exo* C**H**$_3$), 1.05 (d, 3H, CHC**H**$_3$, *J* = 7.5 Hz), 0.80 (s, 3H, *endo* C**H**$_3$); $^{13}$C APT NMR (75 MHz, $CDCl_3$) δ 214.94 (p), 58.39 (a), 50.90 (a), 45.97 (a), 45.06 (p), 37.83 (p), 33.74 (a), 32.12 (p), 28.34 (a), 26.88 (a), 24.50 (p), 21.97 (a), 19.68 (p), 19.42 (a); FT-IR 1712 (C=O) cm$^{-1}$; HRMS M$^+$ 206.1666 (calcd. for $C_{14}H_{22}O$: 206.1672).

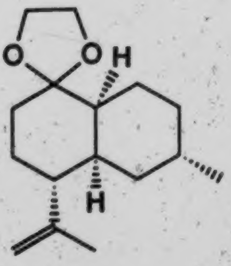
Epimerization of **118**

Ketone **118** (14.6 mg, 0.071 mmol) was dissolved in 3.5 ml of methanol and 0.7 ml of 3 *M* aqueous sodium hydroxide solution was added. The mixture was refluxed for 24 h, cooled to room temperature and extracted with ether. The ether extracts were washed with water, dried, filtered and concentrated to give a mixture of **118** and **119** (14.2 mg, 97% yield in a ratio of 3 : 7 respectively from $^1$H NMR integration).

**(1R, 5R, 6S, 8S)-(-)- (120) and (1S, 5R, 6S, 8S)-(+)-2,2-Ethylenedioxy-8-methyl-5-(1-methylethenyl)bicyclo[4.4.0]decane (121)**



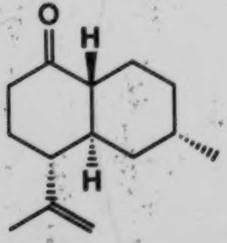
**120**



**121**

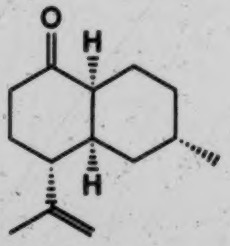
Ethylene glycol (60 µl, 1.1 mmol) and *p*-toluenesulfonic acid (15.5 mg, 0.081 mmol) were added to a solution of **119** (25.5 mg, 0.125 mmol) in 6 ml of benzene. The mixture was heated under reflux with removal of water by a Dean-Stark apparatus for 48 h. The benzene layer was washed with 1 *M* aqueous sodium hydroxide solution, saturated aqueous sodium chloride solution, dried, filtered and concentrated. Flash chromatography with 3% ether in petroleum ether gave **120** (15.0 mg, 0.06 mmol, 48 % yield) as a white solid: $[\alpha]_D^{26}$ = -13.9° (c. 1.50, $CHCl_3$); mp 39-41°C; $^1H$ NMR (300 MHz, $CDCl_3$) δ 4.69 (br s, 2H, $C{=}CH_2$), 3.93 (m, 4H, $OCH_2CH_2O$), 1.95 (m, 1H), 1.25-1.86 (m, 15H), 1.04 (m, 1H), 0.96 (d, 3H, $CHCH_3$, *J* = 7.5 Hz); $^{13}C$ APT NMR (75 MHz, $CDCl_3$) δ 148.39 (=C), 111.09 (=$CH_2$), 109.95 (O-C-O), 65.32, 65.03 (2 x $CH_2$), 52.03, 49.96 (2 x CH), 37.35, 35.30 (2 x $CH_2$), 34.95 (CH), 31.25, 29.25 (2 x $CH_2$), 27.33 (CH), 18.60 ($CH_3$), 18.47 ($CH_2$), 17.93 ($CH_3$); FT-IR 1646 (C=C) $cm^{-1}$; HRMS $M^+$ 250.1931 (calcd. for $C_{16}H_{26}O_2$: 250.1934). Continued elution gave a mixture of **120** and **121** (2.1 mg, 0.008 mmol, 7% yield in a ratio of 22 : 78 from $^1H$ NMR integration) and **121** (11.5 mg, 0.046 mmol, 37% yield) as a white solid: $[\alpha]_D^{26}$ = +27.7° (c. 1.15, $CHCl_3$); mp 60-61°C (ether-petroleum ether); $^1H$ NMR (300 MHz, $CDCl_3$) δ 4.73 (br s, 2H, $C{=}CH_2$), 3.94 (br s, 4H, $OCH_2CH_2O$), 2.36 (m, 1H), 1.92 (m, 1H), 1.40-1.79 (m, 13H), 0.85 (m, 2H), 0.80 (d, 3H, $CHCH_3$, $J$ = 6.5 Hz); $^{13}C$ APT NMR (75 MHz, $CDCl_3$) δ 148.17 (=C), 111.28 (=$CH_2$), 111.13 (O-C-O), 64.23, 64.09 (2 x $CH_2$), 44.76, 42.45 (2 x CH), 37.22 ($CH_2$), 36.26 (CH), 35.10, 30.38, 29.37 (3 x $CH_2$), 26.40 (CH), 23.52 ($CH_2$), 22.94, 18.23 (2 x $CH_3$); FT-IR 1644 (C=C) $cm^{-1}$; HRMS $M^+$ 250.1930 (calcd. for $C_{16}H_{26}O_2$: 250.1934). Anal. Calcd. for $C_{16}H_{26}O_2$: C, 76.74; H, 10.47; found: C, 76.59; H, 10.52.

**(1R, 5R, 6S, 8S)-(-)-8-Methyl-5-(1-methylethenyl)bicyclo[4.4.0]-dec-2-one (122)**



A solution of acetal **120** (9.3 mg, 0.037 mmol) in 1 ml of acetone-water (10 : 1) containing *p*-toluenesulfonic acid (2.3 mg, 0.012 mmol) was refluxed for 3 h. Excess solvent was then removed under reduced pressure. The residue was diluted with ether and the ethereal solution was washed with 1 *M* aqueous sodium hydroxide solution, saturated sodium chloride solution, dried, filtered and concentrated to give a quantitative yield of **122** as a white solid: $[\alpha]_D^{26}$ = -11.12° (c. 0.8, $CHCl_3$); mp 71-73°C; $^1H$ NMR (300 MHz, $CDCl_3$) δ 4.78 (m, 2H, C=$CH_2$), 2.42 (m, 2H), 2.20 (ddd, 1H, $J$ = 12, 11, 4 Hz), 1.44-2.05 (m, 13H), 1.24 (ddd, 1H, $J$ = 13, 11, 4 Hz), 0.92 (d, 3H, $CHCH_3$, $J$ = 7.5 Hz); $^{13}C$ APT NMR (75 MHz, $CDCl_3$) $\delta$ 212.30 (C=O), 146.58 (=C), 112.26 (=$CH_2$), 54.37, 51.55 (2 x CH), 41.43 ($CH_2$), 39.88 (CH), 37.88, 32.52, 30.53 (3 x $CH_2$), 26.99 (CH), 19.57 ($CH_2$), 18.50, 17.60 (2 x $CH_3$); FT-IR 1712 (C=O), 1640 (C=C) $cm^{-1}$; HRMS $M^+$ 206.1674 (calcd. for $C_{14}H_{22}O$: 206.1672).

### (1S, 5R, 6S, 8S)-(+)-8-Methyl-5-(1-methylethenyl)bicyclo[4.4.0]-dec-2-one (123)



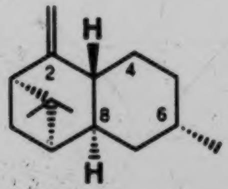
A solution of acetal **121** (26.5 mg, 0.106 mmol) in 1.5 ml of acetone-water (10 : 1) containing *p*-toluenesulfonic acid (6.6 mg, 0.035 mmol) was refluxed for 3.5 h. Excess solvent was then removed by a rotary evaporator. The residue was diluted with ether and the ethereal solution was washed with 1 *M* aqueous sodium hydroxide solution, saturated sodium chloride solution, dried, filtered and concentrated. Flash chromatography with 2-3% ether in petroleum ether gave **123** (18.6 mg, 0.09 mmol, 85% yield) as an oil: $[\alpha]_D^{26}$ = +106.75° (c. 1.17, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 4.72 (m, 2H, C=$CH_2$), 2.72 (ddd, 1H, CHC=, $J$ = 12, 12, 3.5 Hz), 2.56 (ddd, 1H, O=$CCH_{ax}H$, $J$ = 15, 13.5, 6 Hz), 2.40 (dddd, 1H, CHC=O, $J$ = 12, 4.5, 4, 1 Hz), 2.28 (dddd, 1H, O=$CCHH_e$, $J$ = 15, 4, 2, 1 Hz), 2.00 (m, 1H,

$\mathrm{CHC}\mathbf{H}$), 1.90 (m, 1H, $\mathrm{O{=}CCH_2C}\mathbf{H}\mathrm{H}$), 1.48-1.82 (m, 6H, $\mathrm{O{=}CCH_2CH}\mathbf{H}$, $\mathrm{CH_2C}\mathbf{H}_2$, $\mathrm{CHC}\mathbf{H}\mathrm{H}$, $\mathrm{CHCH_3C}\mathbf{H}\mathrm{H}$, $\mathrm{C}\mathbf{H}\mathrm{CH_3}$),1.64 (dd, 3H, $\mathrm{C}\mathbf{H}_3\mathrm{C{=}}$, $J = 1$, 1 Hz), 0.91 (m, 2H, $\mathrm{CHCH}\mathbf{H}$, $\mathrm{CHCH_3CH}\mathbf{H}$), 0.84 (d, 3H, $\mathrm{CHC}\mathbf{H}_3$, $J = 6$ Hz); $^{13}$C APT NMR (75 MHz, $CDCl_3$) $\delta$ 215.15 (C=O), 146.64 (=C), 112.35 (=$CH_2$), 52.65, 42.49, 39.01 (3 x CH), 37.97, 36.21, 34.36, 31.65 (4 x $CH_2$), 26.11 (CH, $CH_2$), 22.79, 18.19 (2 x $CH_3$); FT-IR 1710 (C=O), 1640 (C=C) cm$^{-1}$; HRMS M$^+$ 206.1659 (calcd. for $C_{14}H_{22}O$: 206.1672).

Epimerization of **123**

Ketone **123** (11.0 mg, 0.053 mmol) was dissolved in 2.0 ml of methanol and to this solution was added 0.35 ml of 3 *M* aqueous sodium hydroxide solution. The mixture was reflux for 22 h, cooled to room temperature and extracted with ether. The ether extracts were washed with water, dried, filtered and concentrated to give a mixture of **122** and **123** (8.0 mg, 73% yield in a ratio of 74 : 26 respectively from $^1$H NMR integration).

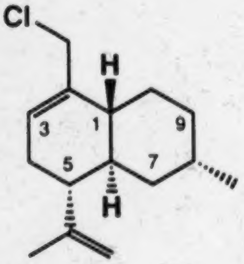
**(1R, 3R, 6S, 8S, 9R)-(+)-6,10,10-Trimethyl-2-methylenetricyclo-[7.1.1.0$^{3,8}$]undecane (124)**



Potassium hydride (291.6 mg, 35% by wt, 2.55 mmol) in a 3-necked flask was washed with benzene (dried, 3 x) under an argon atmosphere. DMSO (1.50 ml) was introduced *via* a syringe and the mixture was stirred at room temperature until the evolution of hydrogen ceased. Methyltriphenylphosphonium bromide (903.9 mg, 2.53 mmol) in 1.50 ml of DMSO was added to the light greenish yellow solution. The resulting bright yellowish green solution was stirred at room temperature for 10 min before use.

Ketone **119** (122.7 mg, 0.6 mmol) in 2 ml of benzene was added to the above solution of methylenetriphenylphosphorane. The resulting dark red solution was stirred at room temperature for 21 h, water was then added. The mixture was extracted with petroleum ether. The extracts were washed with water, dried, filtered and concentrated. The crude product was then passed through a layer of silica gel in a sintered funnel and the silica gel was washed with petroleum ether. The filtrate was concentrated to give **124** (109.1 mg, 0.535 mmol, 90% yield) as an oil: $[\alpha]_D^{26} = +28.83°$ (c. 0.822, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) δ 4.67 (dd, 1H, $\mathrm{C{=}C}\mathbf{H}\mathrm{H}$, *J* = 2, 2 Hz), 4.55 (dd, 1H, $\mathrm{C{=}CH}\mathbf{H}$, *J* = 2, 2 Hz), 2.49 (dd, 1H, $\mathrm{CH_2{=}CC}\mathbf{H}$, *J* = 5.5, 5.5 Hz), 1.97-2.22 (m, 3H), 1.48-1.86 (m, 8H), 1.36 (m, 1H), 1.28 (s, 3H, *exo* $CH_3$), 1.02 (d, 3H, $\mathrm{CHC}\mathbf{H_3}$, *J* = 7 Hz), 0.68 (s, 3H, *endo* $CH_3$); $^{13}$C APT NMR (75 MHz, $CDCl_3$) δ 154.07 (=C), 103.03 (=$CH_2$), 52.88, 46.43 (2 x CH), 43.35 (C), 42.99 (CH), 38.51 ($CH_2$), 34.27 (CH), 32.64 ($CH_2$), 28.46 (CH), 26.95 ($CH_3$), 24.46, 22.62 (2 x $CH_2$), 21.35, 19.51 (2 x $CH_3$); FT-IR 1640 (C=C) cm$^{-1}$; HRMS M$^+$ 204.1888 (calcd. for $C_{15}H_{24}$: 204.1879).

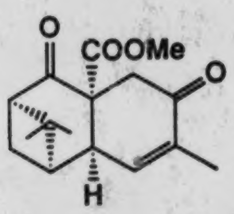
**(1R, 5R, 6S, 8S)-(-)-2-Chloromethyl-8-methyl-5-(1-methylethenyl)bicyclo[4.4.0]dec-2-ene (125)**



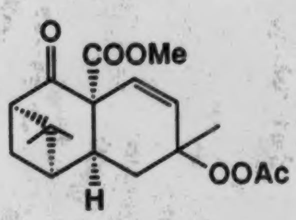
DMSO (33 µl, 0.46 mmol) was added to a solution of phenyl dichlorophosphate (41 µl, 0.276 mmol) in 0.5 ml of dichloromethane at -50°C under an argon atmosphere. Compound **124** (37.5 mg, 0.184 mmol) in 0.5 ml dichloromethane was then added. The reaction mixture was stirred at -50°C to -45°C for 24 h. After this time, 23.7 mg (0.282 mmol) of sodium bicarbonate in 0.5 ml of water was added and the reaction mixture was stirred at 0°C for 3 h. The mixture was extracted with ether and the extracts were washed with water, dried, filtered and concentrated. The crude product was filtered through a layer of silica gel in a sintered funnel and the silica gel was washed with petroleum ether. The filtrate was collected in 2 ml fractions and after concentration compound **125** (26.7 mg, 0.113 mmol, 61% yield) was obtained as a white solid: $[\alpha]_D^{26}$ = -34.21° (c. 0.95, $CHCl_3$); mp 73-75°C (ether-petroleum ether); $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.81 (m, 1H, $CH_2ClC{=}CH$), 4.73 (m, 2H, $C{=}CH_2$), 4.22 (br d, 1H, CHHCl, $J$ = 11 Hz), 3.93 (d, 1H, CHHCl, $J$ = 11 Hz), 1.62 (s, 3H, $=CCH_3$), 0.98 (d, 3H, $CHCH_3$, $J$ = 7.5 Hz); $^{13}C$ APT NMR (75 MHz, $CDCl_3$) δ 147.27, 136.76 (2 x =C), 127.94 (=CH), 112.15 (=$CH_2$), 47.98 ($CH_2Cl$), 47.58, 42.24 (2 x CH), 36.26 ($CH_2$), 35.41 (CH), 32.04, 31.25 (2 x $CH_2$), 27.50 (CH), 23.94 ($CH_2$), 18.41, 17.82 (2 x $CH_3$); FT-IR 1658, 1644 (C=C) $cm^{-1}$; HRMS $M^+$ 240.1465, 238.1490 (calcd. for $C_{15}H_{23}Cl^{37}$: 240.1460; $C_{15}H_{23}Cl^{35}$: 238.1487). Anal. Calcd. for $C_{15}H_{23}Cl$: C, 75.43; H, 9.71; found: C, 75.40; H, 9.82.

## III. TOTAL SYNTHESIS OF SESQUITERPENES: (+)-METHYL LEDESMATE AND (-)-METHYL ZAFRONATE

### (1R, 3R, 8R, 9R)-(+)-3-Carbomethoxy-6,10,10-trimethyltricyclo-[7.1.1.$0^{3,8}$]undec-6-en-2,5-dione (126) and (1R, 3S, 6S(R), 8S, 9R)-3-carbomethoxy-6-peracetoxy-6,10,10-trimethyltricyclo-[7.1.1.$0^{3,8}$]undec-4-en-2-one (127)



**126**

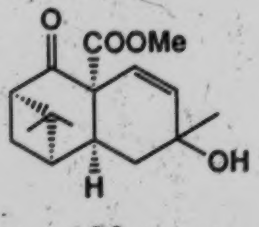


**127**

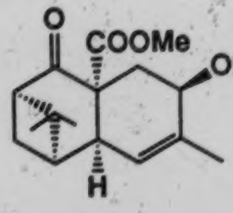
A solution of keto ester **85** (5.5117 g, 0.0249 mol), acetic anhydride (3.5 ml, 0.0373 mol, 1.5 eq), pyridine (2.6 ml, 0.0323 mol, 1.3 eq), catalytic amount of 4-N,N-dimethylaminopyridine and tetraphenylporphine in dichloromethane (250 ml, dried) was bubbled with oxygen for 20 min and was irradiated with two 200W tungsten lamps for 13 h. During this period a gentle stream of oxygen was bubbled through the reaction mixture. After 13 h, the lights were turned off and oxygen was bubbled through the solution for another 5 h. The reaction mixture was then concentrated (100 ml) and washed with saturated aqueous sodium bicarbonate solution (3 x), 1 *M* hydrochloric acid (3 x), saturated copper sulphate solution, saturated sodium chloride solution, dried, filtered and concentrated. The residue was subjected to flash chromatography with 5-25% ether in petroleum ether to give a trace amount of compound **127** (120.5 mg, 0.359 mmol, 1% yield): $^1$H NMR (300 MHz, CDCl$_3$) δ 5.95 (d, 1H, C**H**=CH, *J* = 8 Hz), 4.53 (d, 1H, CH=C**H**, *J* = 8 Hz), 3.84 (s, 3H, OC**H**$_3$), 3.36 (dddd, 1H, CHC**H**, *J* = 12, 5.5, 1.5, 1.5 Hz), 2.68 (dd, 1H, O=CC**H**, *J* = 5.5, 5.5 Hz), 2.55 (dd, 1H, C**H**HCO$_3$CH$_3$, *J* = 15, 5.5 Hz), 2.46 (dddd, 1H, CHC**H**$_{exo}$H, *J* = 11, 5.5, 5.5, 1.5 Hz), 2.17 (dd, 1H, CH**H**CO$_3$CH$_3$, *J* = 15, 12 Hz), 2.09 (s, 3H, COC**H**$_3$), 2.07 (d, 1H, CHCH**H**$_{endo}$, *J* = 11 Hz), 1.97 (ddd, 1H, (CH$_3$)$_2$CC**H**, *J* = 5.5, 5.5, 1.5 Hz), 1.71 (s, 3H, C**H**$_3$), 1.34 (s, 3H, C**H**$_3$), 1.04 (s, 3H, C**H**$_3$); $^{13}$C APT NMR (75 MHz, CDCl$_3$) δ 209.68 (C=O), 172.28, 169.54 (2 x OC=O), 139.48 (=CH), 105.95 (C-O), 105.55 (=CH), 60.58 (C), 57.90 (CH), 53.11 (OCH$_3$), 47.13 (CH), 43.09 (C), 40.31 (CH$_2$), 38.07 (CH), 27.11, 26.95 (2 x CH$_3$), 24.26 (CH$_2$), 22.65, 21.35 (2 x CH$_3$); FT-IR 1731 (C=O, ester), 1712 (C=O, ketone) cm$^{-1}$; HRMS M$^+$ 336.1575 (calcd. for $C_{18}H_{24}O_6$: 336.1573). Continued elution with 25% ether in petroleum ether gave **126** (6.1857g, 0.0224 mol, 90% yield). After recrystalization from dichloromethane-petroleum ether white hexagonal shape crystals of **126** was obtained: $[\alpha]_D^{25}$ = +137.10° (c. 1.55, CHCl$_3$); mp 109-110°C (dichloromethane-petroleum ether); $^1$H NMR (300 MHz, CDCl$_3$) δ 6.47

(dq, 1H, C**H**=CCH$_3$, *J* = 5, 1 Hz), 3.79 (s, 3H, OCH$_3$), 3.60 (m, 1H, CHC**H**), 3.32 (d, 1H, O=CC**H**H, *J* = 18 Hz), 2.80 (dd, 1H, O=CC**H**, *J* = 5.5, 5.5 Hz), 2.67 (d, 1H, O=CCH**H**, *J* = 18 Hz), 2.59 (m, 1H, CHC**H**$_{exo}$H), 2.40 (ddd, 1H, C(CH$_3$)$_2$C**H**, *J* = 5.5, 5.5, 2 Hz), 1.92 (d, 1H, CHCH**H**$_{endo}$, *J* = 11.5 Hz), 1.85 (dd, 3H, CH=CC**H**$_3$, *J* = 2, 1 Hz), 1.45 (s, 3H, *exo* CH$_3$), 1.14 (s, 3H, *endo* CH$_3$); $^{13}$C APT NMR (75 MHz, CDCl$_3$) δ 206.60 (C=O), 194.03 (C=O), 171.56 (OC=O), 144.25 (=CH), 135.83 (=C), 58.28 (CH), 56.63 (C), 53.39 (OCH$_3$), 46.96 (CH), 43.43 (C), 42.33 (CH$_2$), 37.97 (CH), 26.94 (CH$_3$), 25.60 (CH$_2$), 21.47, 16.18 (2 x CH$_3$); FT-IR 1735 (C=O, ester), 1711 (C=O, ketone), 1678 (C=O, conjugated ketone) cm$^{-1}$; HRMS M$^+$ 276.1355 (calcd. for $C_{16}H_{20}O_4$: 276.1362). Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.53; H, 7.30; found: C, 69.55; H, 7.33.

**(1R, 3R, 5R, 8R, 9R)-(+)-3-Carbomethoxy-5-hydroxy-6,10,10-trimethyltricyclo[7.1.1.0$^{3,8}$]undec-6-en-2-one (116) and (1R, 3S, 6S(R), 8S, 9R)-3-carbomethoxy-6-hydroxy-6,10,10-trimethyltricyclo[7.1.1.0$^{3,8}$]undec-4-en-2-one (129)**



**129**

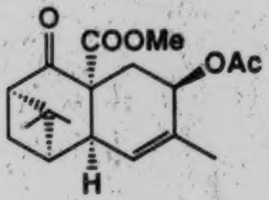


**116**

A solution of keto ester **85** (74.1 mg, 0.283 mmol) and a catalytic amount of tetraphenylporphine in dichloromethane (100 ml, dried) was bubbled with oxygen for 20 min and irradiated with two 200W tungsten lamp for 3 h. During irradiation, a gentle stream of oxygen was bubbled through the reaction mixture. After 3 h, the solvent was evaporated. The residue was dissolved in 2 ml of dichloromethane and cooled to 0°C. Triphenylphosphine (91.8 mg, 0.35 mmol) was then added to the solution. After 10 min, the dichloromethane was evaporated and the residue was separated by flash chromatography on silica gel eluting with 18-32% ether in petroleum ether to give compound **129** (2.0 mg, 0.007 mmol, 2% yield): $^1$H NMR (300 MHz, $CDCl_3$) δ 5.92 (dd, 1H, **CH**=CH, *J* = 10, 1 Hz), 5.82 (dd, 1H, CH=**CH**, *J* = 10, 1 Hz), 3.79 (s, 3H, $O\mathbf{CH_3}$), 3.22 (m, 1H, CHC**H**), 2.67 (dd, 1H, O=CC**H**, *J* = 5, 5 Hz), 2.45 (dddd, 1H, $CHC\mathbf{H}_{exo}H$, *J* = 11, 5, 5, 1 Hz), 2.28 (d, 1H, $CHCH\mathbf{H}_{endo}$, *J* = 11 Hz), 2.26 (m, 1H, $(CH_3)_2CC\mathbf{H}$), 1.90 (m, 2H, $\mathbf{CH_2}COH$), 1.37 (s, 3H, $\mathbf{CH_3}$), 1.31 (s, 3H, $\mathbf{CH_3}$), 1.05 (s, 3H, $\mathbf{CH_3}$); FT-IR 3480 (OH), 1731 (C=O, ester), 1711 (C=O, ketone) cm$^{-1}$; HRMS $M^+-CH_3OH$ 246.1253 (calcd. for $C_{15}H_{18}O_3$: 246.1256); CIMS $M^+$ 278 ($C_{16}H_{22}O_4$). Further elution with 45% ether in petroleum ether gave a quantitative yield of **116**: $[\alpha]_D^{22}$ = +58.57° (c. 0.84, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) δ 5.24 (m, 1H, $\mathbf{CH}=CCH_3$), 4.11 (m, 1H, **CH**OH), 3.81 (s, 3H, $O\mathbf{CH_3}$), 3.44 (m, 1H, CHC**H**), 2.82 (dd, 1H, $CHOHC\mathbf{H}_eH$, *J* = 13, 5.5 Hz), 2.70 (dd, 1H, O=CC**H**, *J* = 5.5, 5.5 Hz), 2.43 (m, 1H, $CHC\mathbf{H}_{exo}H$), 2.11 (ddd, 1H, $C(CH_3)_2\mathbf{CH}$, *J* = 5.5, 5.5, 2 Hz), 1.96 (d, 1H, $CHCH\mathbf{H}_{endo}$, *J* = 11 Hz), 1.81 (m, 4H, $CHC=\mathbf{CH_3}$, $CHOHCH\mathbf{H}_{ax}$), 1.70 (d, 1H, O**H**, *J* = 6 Hz), 1.39 (s, 3H, *exo* $\mathbf{CH_3}$), 0.99 (s, 3H, *endo* $\mathbf{CH_3}$); $^{13}$C APT NMR (75 MHz, $CDCl_3$) δ 208.45 (C=O), 171.52 (OC=O), 138.08 (=C), 124.61 (=CH), 66.67, 58.83 (2 x CH), 56.91 (C), 53.07 ($OCH_3$), 46.60

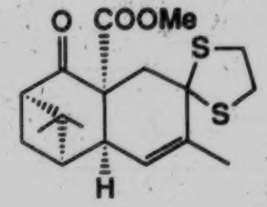
(CH), 43.38 (C), 39.69 ($CH_2$), 36.11 (CH), 27.05 ($CH_3$), 25.05 ($CH_2$), 21.54, 18.83 (2 x $CH_3$); FT-IR 3280 (OH), 1724 (C=O, ester), 1705 (C=O, ketone) $cm^{-1}$; HRMS $M^+$ 278.1516 (calcd. for $C_{16}H_{22}O_4$: 278.1519).

**(1R, 3R, 5R, 8R, 9R)-(+)-5-Acetoxy-3-carbomethoxy-6,10,10-trimethyltricyclo[7.1.1.0$^{3,8}$]undec-6-en-2-one (130)**



To a mixture of **116** (13.7 mg, 0.049 mmol) and pyridine (0.4 ml) was added 0.2 ml of acetic anhydride under argon atmosphere at room temperature. The reaction was stirred overnight and 0.4 ml of methanol was then added. After 1 h, water was added and the mixture was extracted twice with ether. The ether extracts were washed with 1 *M* hydrochloric acid, saturated sodium chloride solution, dried, filtered and concentrated. Flash chromatography of the residue with 10-20% ether in petroleum ether gave **130** (15.0 mg, 0.047 mmol, 95% yield): $[\alpha]_D^{22} = +41.93°$ (c. 1.5, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 5.35 (m, 2H, $C\mathbf{H}{=}CCH_3$, $C\mathbf{H}OCOCH_3$), 3.85 (s, 3H, $OC\mathbf{H}_3$), 3.46 (br s, 1H, $CHC\mathbf{H}$), 2.83 (dd, 1H, $CHOCOCH_3C\mathbf{H}_eH$, $J = 13, 5.5$ Hz), 2.71 (dd, 1H, $O{=}CC\mathbf{H}$, $J = 5.5, 5.5$ Hz), 2.46 (m, 1H, $CHC\mathbf{H}_{exo}H$), 2.23 (ddd, 1H, $C(CH_3)_2C\mathbf{H}$, $J = 5.5, 5.5, 2$ Hz), 2.08 (s, 3H, $COC\mathbf{H}_3$), 1.93 (d, 1H, $CHCH\mathbf{H}_{endo}$, $J = 11$ Hz), 1.86 (dd, 1H, $CHOCOCH_3CH\mathbf{H}_{ax}$, $J = 13, 10.5$ Hz), 1.70 (m, 3H, $CH{=}CC\mathbf{H}_3$), 1.40 (s, 3H, *exo* $CH_3$), 1.02 (s, 3H, *endo* $CH_3$); $^{13}C$ APT NMR (75 MHz, $CDCl_3$) δ 208.07 (C=O), 171.28 (OC=O), 170.39 (OC=O), 135.04 (=C), 126.08 (=CH), 68.69 (CHOAc), 58.77 (CH), 56.20 (C), 53.21 ($OCH_3$), 46.54 (CH), 43.32 (C), 36.05 (CH), 35.87 ($CH_2$), 27.01 ($CH_3$), 25.05 ($CH_2$), 21.45, 20.99, 18.85 (3 x $CH_3$); FT-IR 1741 (C=O, ester), 1711 (C=O, ketone) $cm^{-1}$; HRMS $M^+$ 320.1625 (calcd. for $C_{18}H_{24}O_5$: 320.1624).

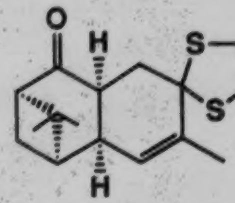
**(1R, 3R, 8R, 9R)-(-)-3-Carbomethoxy-5,5-ethylenedithio-6,10,10-trimethyltricyclo[7.1.1.0$^{3,8}$]undec-6-en-2-one (131)**



At -10°C, 0.1 ml (1.19 mmol, 1.06 eq) of 1,2-ethanedithiol and boron trifluoride etherate (56 µl, 0.447 mmol, 0.4 eq) were added to a solution of enone **126** (308.8 mg, 1.12 mmol) in dichloromethane (5 ml, dried) under an atmosphere of argon. The reaction mixture was stirred for 76 h and 1 ml of 1 *M* aqueous sodium hydroxide solution was then added. The organic layer was separated, washed with 1 *M* aqueous sodium hydroxide solution (3 x), dried, filtered and concentrated. Flash chromatography of the residue with 12-25% ether in petroleum ether gave **131** (246.9 mg, 0.7 mmol, 98% yield based on consumed starting material) as a white solid: $[\alpha]_D^{28}$ = -60.2° (c. 0.804, $CHCl_3$); mp 143-145°C ($CH_2Cl_2$-petroleum ether); $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.41 (dq, 1H, $CH=CCH_3$, $J$ = 4, 1 Hz), 3.82 (s, 3H,

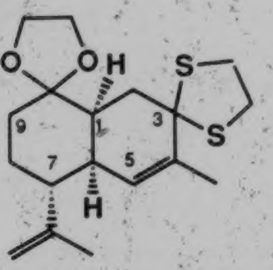
$OCH_3$), 3.75 (m, 1H, CHC**H**), 3.44 (m, 1H, SC**H**HCH$_2$S), 3.31 (m, 3H, $S_2$CCH**H**, SCH**H**CH$_2$S), 3.15 (m, 1H, SCH**H**CH$_2$S), 2.71 (dd, 1H, O=CC**H**, *J* = 6, 6 Hz), 2.39 (m, 1H, CHC**H**$_{exo}$H), 2.37 (d, 1H, $S_2$CC**H**H, *J* = 15 Hz), 2.22 (ddd, 1H, C(CH$_3$)$_2$C**H**, *J* = 6, 6, 2 Hz), 2.01 (dd, 3H, CH=CC**H**$_3$, *J* = 2, 1 Hz), 1.77 (d, 1H, CHCH**H**$_{endo}$, *J* = 11 Hz), 1.36 (s, 3H, *exo* C**H**$_3$), 0.86 (s, 3H, *endo* C**H**$_3$); $^{13}$C APT NMR (75 MHz, CDCl$_3$) δ 206.69 (C=O), 170.67 (OC=O), 135.01 (=C), 129.03 (=CH), 66.69 ($S_2$C), 58.85 (CH), 57.16 (C), 52.84 (OCH$_3$), 48.60 (CH$_2$), 46.66 (CH), 41.59 (C), 40.79, 39.15 (2 x CH$_2$), 34.90 (CH), 26.48 (CH$_3$), 24.91 (CH$_2$), 21.81, 20.10 (2 x CH$_3$); FT-IR 1712 (C=O) cm$^{-1}$; HRMS M$^+$ 352.1170 (calcd. for $C_{18}H_{24}O_3S_2$: 352.1168). Anal. Calcd. for $C_{18}H_{24}O_3S_2$: C, 61.34; H, 6.87; S, 18.16; found: C, 61.32; H, 6.84; S, 18.46. Continued elution recovered starting material **126** (111.3 mg, 0.404 mmol).

### (1R, 3S, 8R, 9R)-(-)-5,5-Ethylenedithio-6,10,10-trimethyltricyclo-[7.1.1.0$^{3,8}$]undec-6-en-2-one (132)

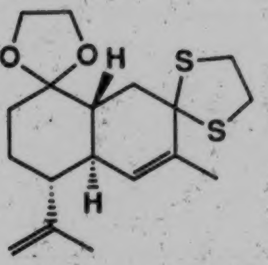


Keto ester **131** (4.798 g, 0.0136 mol) was dissolved in 33 ml 2,4,6-collidine under an atmosphere of argon. Anhydrous lithium iodide (14.252 g, 0.106 mol) and then water (1.96 ml, 0.109 mol) were introduced to the stirred solution. The mixture was heated under reflux for 3 h , then cooled to room temperature, poured into cold 1 *M* hydrochloric acid and extracted with ether. The extracts were washed with ice-cold 1 *M* hydrochloric acid and water, dried, filtered and concentrated. The residue was subjected to flash chromatography on silica gel eluting with 6% ether in petroleum ether to give **132** (3.640 g, 0.0124 mol, 91% yield) as a white solid: $[\alpha]_D^{25} = -145.49°$ (c. 0.91, $CHCl_3$); mp 161-162°C (ether-petroleum ether); $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.33 (dq, 1H, C**H**=$CCH_3$, *J* = 3, 1.5 Hz), 3.20-3.46 (m, 4H, $SC\mathbf{H}_2C\mathbf{H}_2S$), 3.03 (ddd, 1H, C**H**C=O, *J* = 13 ,9, 6 Hz), 2.74 (m, 1H, CHC**H**), 2.61 (m, 2H, O=CC**H**, $S_2CC$H**H**), 2.40 (m, 1H, CHC$\mathbf{H}_{exo}$H), 2.13 (m, 2H, $C(CH_3)_2C$**H**, $S_2CC$H**H**), 2.01 (dd, 3H, CH=CC$\mathbf{H}_3$, *J* = 2.5, 1.5 Hz), 1.65 (d, 1H, CHCH$\mathbf{H}_{endo}$, *J* = 11 Hz), 1.36 (s, 3H, *exo* $CH_3$), 0.91 (s, 3H, *endo* $CH_3$); $^{13}C$ APT NMR (75 MHz, $CDCl_3$) δ 214.62 (C=O), 137.65 (=C), 128.59 (=CH), 67.55 ($S_2C$), 58.44, 46.66 (2 x CH), 46.02 ($CH_2$), 43.39 (CH), 41.13 (C), 40.49, 39.59 (2 x $CH_2$), 33.22 (CH), 25.92 ($CH_3$), 23.56 ($CH_2$), 21.78, 20.26 (2 x $CH_3$); FT-IR 1696 (C=O) $cm^{-1}$; HRMS $M^+$ 294.1122 (calcd. for $C_{16}H_{22}OS_2$: 294.1114). Anal. Calcd. for $C_{16}H_{22}OS_2$: C, 65.28; H, 7.54; S, 21.74; found: C, 65.15; H, 7.47; S, 21.97.

### (1S, 6R, 7R)-(-)- (133) and (1R, 6R, 7R)-(+)-10,10-Ethylenedioxy-3,3-ethylenedithio-4-methyl-7-(1-methylethenyl)bicyclo[4.4.0]-dec-4-ene (134)



**133**

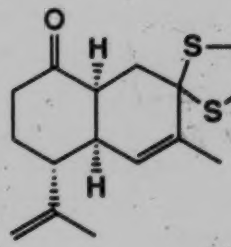


**134**

Ethylene glycol (0.1 ml, 1.79 mmol) and *p*-toluenesulfonic acid (32.5 mg, 0.171 mmol) were added to a solution of **132** (125.4 mg, 0.426 mmol) in 10 ml of benzene. The mixture was heated under reflux with removal of water by a Dean-Stark apparatus for 24 h. The benzene layer was washed twice with 1 *M* aqueous sodium hydroxide solution, saturated sodium chloride solution, dried, filtered and concentrated. Flash chromatography with 3-5% ether in petroleum ether gave acetal **133** (113.0 mg, 0.334 mmol, 78% yield) as a white solid: $[\alpha]_D^{24}$ = -97.5° (c. 0.8, $CHCl_3$); mp 134-135°C (dichloromethane-petroleum ether); $^1$H NMR (300 MHz, $CDCl_3$) δ 5.48 (dq, 1H, CH=$CCH_3$, *J* = 5, 1 Hz), 4.75 (m, 2H, C=$CH_2$), 3.91-4.08 (m, 4H, $OCH_2CH_2O$), 3.21-3.48 (m, 4H, $SCH_2CH_2S$), 1.93 (dd, 3H, CH=$CCH_3$, *J* = 1, 1 Hz), 1.69 (dd, 3H, $CCH_3$=$CH_2$, *J* = 1, 1 Hz); $^{13}$C APT NMR (75 MHz, $CDCl_3$) δ 147.18, 135.02 (2 x =C), 130.10 (=CH), 111.45 (=$CH_2$), 109.78 (O-C-O), 70.14 ($S_2C$), 64.21, 64.04 (2 x $CH_2$), 46.72, 41.42 (2 x CH), 41.07, 41.01, 40.06 (3 x $CH_2$), 36.74 (CH), 31.20, 29.12 (2 x $CH_2$), 19.88, 19.67 (2 x $CH_3$); FT-IR 1641 (C=C) $cm^{-1}$; HRMS $M^+$ 338.1372 (calcd. for $C_{18}H_{26}O_2S_2$: 338.1376). Anal. Calcd. for $C_{18}H_{26}O_2S_2$: C, 63.88; H, 7.75; S, 18.91; found: C, 63.98; H, 7.51; S, 18.60. Continued elution with 5% ether in petroleum ether gave a mixture of **133** and **134** (11.5 mg, 0.034

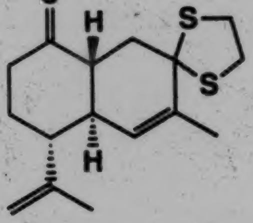
mmol, 8% yield in the ratio of 63 : 37 respectively from $^1$H NMR integration) and acetal **134** (17.3 mg, 0.051 mmol, 12% yield): $[\alpha]_D^{24}$ = +31° (c. 1.50, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.39 (m, 1H, $CH=CCH_3$), 4.83 (m, 1H, C=CH**H**), 4.76 (br s, 1H, C=C**H**H), 3.92-4.05 (m, 4H, $OCH_2CH_2O$), 3.21-3.47 (m, 4H, $SCH_2CH_2S$), 1.94 (dd, 3H, $CH=CCH_3$, $J$ = 2.5, 1 Hz), 1.67 (br s, 3H, $CCH_3=CH_2$); $^{13}$C APT NMR (75 MHz, $CDCl_3$) $\delta$ 147.27, 135.56 (2 x =C), 128.91 (=CH), 112.36 (=$CH_2$), 109.19 (O-C-O), 70.10 ($S_2C$), 65.20, 65.08 (2 x $CH_2$), 49.77, 46.67 (2 x CH), 42.45, 41.39, 40.34 (3 x $CH_2$), 40.08 (CH), 34.89, 29.48 (2 x $CH_2$), 19.77, 19.08 (2 x $CH_3$); FT-IR 1640 (C=C) cm$^{-1}$; HRMS M$^+$ 338.1375 (calcd. for $C_{18}H_{26}O_2S_2$: 338.1376).

### (1S, 5R, 6R)-(-)-9,9-Ethylenedithio-8-methyl-5-(1-methylethenyl)bicyclo[4.4.0]dec-7-en-2-one (135)



A solution of acetal **133** (35.3 mg, 0.104 mmol) in 2 ml of acetone-water (13 : 1) containing *p*-toluenesulfonic acid (6.5 mg, 0.034 mmol) was refluxed for 8 h. Excess solvent was then removed under reduced pressure. The residue was diluted with ether and the ethereal solution washed twice with 1 *M* aqueous sodium hydroxide solution, saturated sodium chloride solution, dried, filtered and concentrated. Flash chromatography of the residue with 5-10% ether in petroleum ether gave **135** (30.6 mg, 0.104 mmol, 100% yield) as a white solid: $[\alpha]_D^{23}$ = -77.78° (c. 0.765, $CHCl_3$); mp 146-147°C (dichloromethane-petroleum ether); $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.47 (dq, 1H, CH=C$CH_3$, *J* = 5, 1.5 Hz), 4.86 (m, 1H, C=CH**H**), 4.82 (br s, 1H, C=C**H**H), 3.38 (m, 3H, SCHHC$H_2$S), 3.22 (m, 1H, SCH**H**C$H_2$S), 2.93 (ddd, 1H, CHC=O, *J* = 13, 6, 3 Hz), 2.42 (m, 4H, O=CC**H**$_2$, CHC**H**, $S_2$CC**H**H), 2.33 (ddd, 1H, $CH_2$C**H**, *J* = 12, 12, 3 Hz), 2.20 (dd, 1H, $S_2$CCH**H**, *J* = 13, 3 Hz), 1.97 (dd, 3H, CH=CC**H**$_3$, *J* = 1.5, 1.5 Hz), 1.88 (m, 1H, $CH_2$CH**H**), 1.73 (m, 1H, $CH_2$C**H**H), 1.72 (dd, 3H, C$CH_3$=$CH_2$, *J* = 1.5, 1 Hz); $^{13}C$ APT NMR (75 MHz, $CDCl_3$) δ 212.78 (C=O), 145.83, 135.53 (2 x =C), 128.28 (=CH), 112.47 (=$CH_2$), 68.78 ($CS_2$), 49.23, 46.76 (2 x CH), 42.96, 41.23, 39.99, 39.09 (4 x $CH_2$), 39.02 (CH), 30.71 ($CH_2$), 19.97, 19.58 (2 x $CH_3$); FT-IR 1707 (C=O), 1645 (C=C) $cm^{-1}$; HRMS $M^+$ 294.1112 (calcd. for $C_{16}H_{22}OS_2$: 294.1114). Anal. Calcd. for $C_{16}H_{22}OS_2$: C, 65.28; H, 7.54; S, 21.74; found: C, 65.23; H, 7.37; S, 21.88.

### (1R, 5R, 6R)-(+)-9,9-Ethylenedithio-8-methyl-5-(1-methylethenyl)bicyclo[4.4.0]dec-7-en-2-one (79)

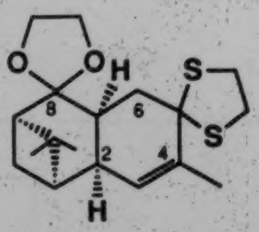


*p*-Toluenesulfonic acid (3.4 mg, 0.018 mmol) was added to a solution of acetal **134** (12.2 mg, 0.036 mmol) in 2 ml of acetone-water (10 : 1). The mixture was then heated under refluxed for 22 h. Excess solvent was then removed under reduced pressure. The residue was diluted with ether and the ethereal solution was washed twice with 1 *M* aqueous sodium hydroxide solution, saturated sodium chloride solution, dried, filtered and concentrated. Flash chromatography of the residue with 3-4% ether in petroleum ether gave **79** (8.9 mg, 0.03 mmol, 84% yield) as a white solid: $[\alpha]_D^{23} = +81.08°$ (c. 1.09, $CHCl_3$); mp 139-140°C (dichloromethane-petroleum ether); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 5.42 (m, 1H, $C\mathbf{H}{=}CCH_3$), 4.90 (m, 1H, $C{=}C\mathbf{H}H$), 4.83 (br s, 1H, $C{=}CH\mathbf{H}$), 3.32 (m, 4H, $SC\mathbf{H}_2C\mathbf{H}_2S$), 2.69 (dd, 1H, $S_2CC\mathbf{H}_eH$, $J = 14$, 2 Hz), 2.47 (m, 3H, $C\mathbf{H}C{=}O$, $O{=}CC\mathbf{H}_2$), 2.30 (ddd, 1H, $C\mathbf{H}C{=}CH_2$, $J = 12$, 12, 3.5 Hz), 2.16 (m, 1H, $CHC\mathbf{H}$), 2.07 (dd, 1H, $S_2CCH\mathbf{H}_{ax}$, $J = 14$, 12 Hz), 2.01 (m, 1H, $CH_2CH\mathbf{H}$), 1.96 (dd, 3H, $CH{=}CC\mathbf{H}_3$, $J = 2$, 1.5 Hz), 1.78 (m, 1H, $CH_2CH\mathbf{H}$),1.67 (dd, 3H, $C\mathbf{H}_3C{=}CH_2$, $J = 1.5$, 0.5 Hz); $^{13}C$ APT NMR (75 MHz, $CDCl_3$) $\delta$ 210.40 (C=O), 145.65, 136.49 (2 x =C), 127.95 (=CH), 113.44 (=$CH_2$), 69.40 ($S_2C$), 50.93, 49.49, 44.14 (3 x CH), 42.61, 41.35, 40.91, 40.10, 32.37 (5 x $CH_2$), 19.80, 18.99 (2 x $CH_3$); FT-IR 1716 (C=O) $cm^{-1}$; HRMS $M^+$ 294.1120 (calcd. for $C_{16}H_{22}OS_2$: 294.1114). Anal. Calcd. for $C_{16}H_{22}OS_2$: C, 65.28; H, 7.54; S, 21.74; found: C, 65.49; H, 7.67; S, 21.90.

Epimerization of **135**

Ketone **135** (10.3 mg, 0.035 mmol) was dissolved in 2.5 ml of methanol and 0.5 ml of 1 *M* aqueous sodium hydroxide solution was added. After refluxing for 17 h, water was added and the mixture was extracted with ether. The extracts were washed with saturated aqueous sodium chloride, dried, filtered and concentrated to give **79** (10.0 mg, 97% yield).

### (1R, 2R, 7S, 9R)-(-)-8,8-Ethylenedioxy-5,5-ethylenedithio-4,10,10-trimethyltricyclo[7.1.1.0$^{2,7}$]undec-4-ene (136)



Ethylene glycol (0.16 ml, 2.91 mmol) and *p*-toluenesulfonic acid (6 mg, 0.032 mmol) were added to a solution of **132** (94.9 mg, 0.323 mmol) in 16 ml of benzene. The mixture was heated under reflux with removal of water by a Dean-Stark apparatus for 3 h. The benzene layer was washed twice with 1 *M* aqueous sodium hydroxide solution, saturated sodium chloride solution, dried, filtered and concentrated. Flash chromatography with 0-7% ether in petroleum ether gave acetal **136** (20.6 mg, 0.061 mmol): $[\alpha]_D^{26}$ = -176.24° (c. 0.888, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.21 (m, 1H, C**H**=$CCH_3$), 3.90 (m, 4H, $OCH_2CH_2O$), 3.29 (m, 4H, $SCH_2CH_2S$), 2.71 (m, 2H, CHCH=, $CH_2$C**H**), 2.29 (m, 2H, $S_2CC$**H**$_2$), 2.12 (m, 1H, CHC**H**$_{exo}$H), 2.01 (dd, 1H, $O_2CC$**H**, *J* = 5.5, 5.5 Hz), 1.97 (dd, 3H, CH=CC**H**$_3$, *J* = 1.5, 1 Hz), 1.84 (br dd, 1H, $C(CH_3)_2C$**H**, *J* = 5.5, 5.5 Hz), 1.28 (d, 1H, CHCH**H**$_{endo}$, $J = 11$ Hz), 1.23 (s, 3H, *exo* **CH$_3$**), 1.01 (s, 3H, *endo* **CH$_3$**); $^{13}$C APT NMR (75 MHz, CDCl$_3$) δ 137.54 (=C), 130.08 (=CH), 113.58 (O-C-O), 68.56 (S$_2$C), 64.39, 64.04 (2 x CH$_2$), 50.44, 46.50 (2 x CH), 45.54, 40.36 (2 x CH$_2$), 40.16 (CH), 39.77 (CH$_2$), 38.64 (C), 34.82 (CH), 26.78 (CH$_3$), 23.59 (CH$_2$), 22.60, 20.06 (2 x CH$_3$); HRMS M$^+$ 338.1373 (calcd. for $C_{18}H_{26}O_2S_2$: 338.1376). Further elution gave a mixture of acetal **133** and **136** (6.9 mg). Continued elution recovered starting material, ketone **132** (68.6 mg, 0.23 mmol).

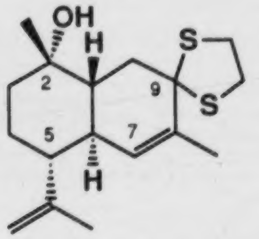
Deacetalization of **136**

*p*-Toluenesulfonic acid (2.6 mg, 0.014 mmol) was added to a solution of acetal **136** (12.6 mg, 0.037 mmol) in 2 ml of moist benzene and the mixture was refluxed for 15 min. The mixture was then washed with 1 *M* aqueous sodium hydroxide solution (2 x), saturated sodium chloride solution, dried, filtered and concentrated. Flash chromatography on silica gel using 3% ether in petroleum ether as eluant gave ketone **132** (10.0 mg, 0.034 mmol, 91% yield).

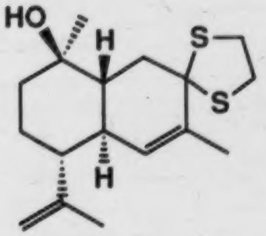
**133** and **134** from **136**

*p*-Toluenesulfonic (2.5 mg, 0.013 mmol) acid was dissolved in 2 ml of benzene and refluxed for 2 h with removal of water by a Dean-Stark apparatus. Then 8.6 mg (0.025 mmol) of acetal **136** in 1 ml of dried benzene was added and the mixture was refluxed again with removal of water for 1 h. The mixture was washed with 1 *M* aqueous sodium hydroxide solution (2 x), saturated aqueous sodium chloride solution, dried, filtered and concentrated. Flash chromatography with 0-3% ether in petroleum ether gave a mixture of **133** and **134** (5.1 mg, 0.015 mmol, 59% yield) in a ratio of 4 : 1 respectively.

### (1R, 2S, 5R, 6R)-(+)- (137) and (1R, 2R, 5R, 6R)-(-)-9,9-Ethylenedithio-2,8-dimethyl-5-(1-methylethenyl)bicyclo[4.4.0]-dec-7-en-2-ol (138)



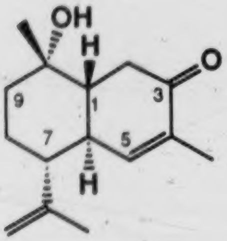
**137**



**138**

At -78°C, to a suspension of cerium chloride (130.4 mg) in 15 ml of tetrahydrofuran (dried) was added a solution of ketone **79** (343.7 mg, 1.17 mmol) in 5 ml of tetrahydrofuran (dried) under an argon atmosphere. The mixture was stirred for 20 min at -78 °C. Then at 0°C, 1.70 ml (2.34 mmol ) of methyllithium (1.4 M solution in ether) was added dropwise. After 4.5 h, water and 5% hydrochloric acid were added until all the cerium salt dissolved. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 x 10 ml). The combined organic layer was dried, filtered and concentrated. Flash chromatography of the residue with 15-40 % ether in petroleum ether recovered starting material (55.0 mg, 0.187 mmol) and gave alcohol **137** (152.3 mg, 0.491 mmol, 50% yield based on consumed ketone) as a white solid: $[\alpha]_D^{26} = +11.86°$ (c. 1.94, $CHCl_3$); mp 113-114°C (ether-petroleum ether); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 5.41 (m, 1H, $C\mathbf{H}{=}CCH_3$), 4.82 (m, 1H, $C{=}C\mathbf{H}H$), 4.74 (br s, 1H, $C{=}CH\mathbf{H}$), 3.33 (m, 4H, $SC\mathbf{H}_2C\mathbf{H}_2S$), 2.47 (dd, 1H, $S_2CC\mathbf{H}_eH$, $J$ = 13, 2 Hz), 2.17 (m, 1H, $CHC\mathbf{H}$), 2.09 (dd, 1H, $S_2CCH\mathbf{H}_{ax}$, $J$ = 13, 12 Hz), 1.93 (dd, 3H, $CH{=}CC\mathbf{H}_3$, $J$ = 2.5, 1.5 Hz), 1.76 (m, 3H), 1.68 (br s, 3H, $C\mathbf{H}_3C{=}CH_2$), 1.46 (m, 3H), 1.27 (s, 3H, $C\mathbf{H}_3$), 1.10 (s, 1H, O$\mathbf{H}$); $^{13}C$ APT NMR (75 MHz, $CDCl_3$) $\delta$ 147.74, 135.19 (2 x =C), 129.38 (=CH), 112.08 (=$CH_2$), 70.70, 70.38 (2 x C), 50.46, 47.90 (2 x CH), 43.98, 41.36, 40.27, 40.08 (4 x $CH_2$), 37.61 (CH), 28.22 ($CH_3$), 27.74 ($CH_2$), 19.67, 19.12 (2 x $CH_3$); FT-IR 3440 (OH), 1640 (C=C) $cm^{-1}$; HRMS $M^+$ 310.1422 (calcd. for $C_{17}H_{26}OS_2$: 310.1427). Anal. Calcd. for $C_{17}H_{26}OS_2$: C, 65.78; H, 8.45; S, 20.64; found: C, 65.55; H, 8.29; S, 20.33. Continued elution with 40% ether in petroleum ether gave alcohol **138** (120.5 mg, 0.389 mmol, 40% yield based on consumed ketone) as a white solid: $[\alpha]_D^{23} = -31.52°$ (c. 0.66, $CHCl_3$); mp 65-66°C (dichloromethane-petroleum ether); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 5.38 (m, 1H, $C\mathbf{H}{=}CCH_3$), 4.83 (m, 1H, $C{=}C\mathbf{H}H$), 4.75 (br s, 1H, $C{=}CH\mathbf{H}$), 3.34 (m, 4H, $SC\mathbf{H}_2C\mathbf{H}_2S$), 2.60 (dd, 1H, $S_2CC\mathbf{H}_eH$, $J$ = 13, 2 Hz), 1.94 (dd, 3H, $CH{=}CC\mathbf{H}_3$, $J$ = 2, 1 Hz), 1.87 (m, 4H), 1.64 (dd, 3H, $C\mathbf{H}_3C{=}CH_2$, $J$ = 1.5, 0.5 Hz), 1.52 (m, 4H), 1.36 (s, 1H, O$\mathbf{H}$), 1.16 (s, 3H, $C\mathbf{H}_3$); $^{13}C$ APT NMR (75 MHz, $CDCl_3$) $\delta$ 147.07, 135.70 (2 x =C), 128.94 (=CH), 112.40 (=$CH_2$), 71.52, 70.44 (2 x C), 50.46, 49.79 (2 x CH), 43.75, 42.24, 41.17, 40.27 (4 x $CH_2$), 39.93 (CH), 29.90 ($CH_2$), 20.80, 19.73, 19.21 (3 x $CH_3$); FT-IR 3416 (OH), 1640 (C=C) cm $^{-1}$; HRMS $M^+$ 310.1424 (calcd. for $C_{17}H_{26}OS_2$: 310.1427).

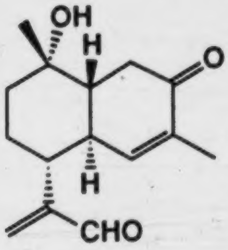
### (1R 6R, 7R, 10S)-(-)-10-Hydroxy-4,10-dimethyl-7-(1-methylethenyl)bicyclo[4.4.0]dec-4-en-3-one (141)



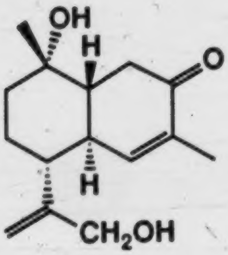
To a solution of **137** (102.8 mg, 0.332 mmol) in 7.70 ml methanol-water (10 : 1) was added 757 mg (3.27 mmol) $Ag_2O$. The mixture was refluxed for 19 h and silver mirror was formed around the flask. The mixture was then filtered through a layer of silica gel in sintered funnel and concentrated. The filtration produre was repeated and the brown solution was extracted with ether (3 x). The ether extracts were dried, filtered and concentrated. Flash chromatography with 20-45% ether in petroleum ether gave **141** (55.1 mg, 0.235 mmol, 71% yield) as a white solid: $[\alpha]_D^{23} = -25.14°$ (c. 1.24, $CHCl_3$); mp 131°C (dichloromethane-petroleum ether); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 6.63 (m, 1H, $C\mathbf{H}{=}CCH_3$), 4.90 (m, 1H, $C{=}CH\mathbf{H}$), 4.82 (br s, 1H, $C{=}CH\mathbf{H}$), 2.63 (dd, 1H, $O{=}CC\mathbf{H}_eH$, $J = 16.5, 3.5$ Hz), 2.53 (m, 1H, $CHC\mathbf{H}$), 2.41 (dd, 1H, $O{=}CCH\mathbf{H}_{ax}$, $J = 16.5, 13.5$ Hz), 187 (m, 2H), 1.75 (dd, 3H, $CH{=}CC\mathbf{H}_3$, $J = 2.5, 1$ Hz), 1.73 (dd, 3H, $C\mathbf{H}_3C{=}CH_2$, $J = 1.5, 1$ Hz), 1.72 (m, 2H), 1.55 (m, 2H), 1.21 (s, 3H, $C\mathbf{H}_3$), 1.15 (s, 1H, $O\mathbf{H}$);

$^{13}$C APT NMR (75 MHz, $CDCl_3$) δ 200.44 (C=O), 148.35 (=CH), 147.00, 134.90 (2 x =C), 112.94 (=$CH_2$), 70.02 (C-OH), 49.85, 49.37 (2 x CH), 39.87, 38.35 (2 x $CH_2$), 38.26 (CH), 28.03 ($CH_3$), 27.37 ($CH_2$), 19.17, 15.67 (2 x $CH_3$); FT-IR 3448 (OH), 1661 (C=O, conjugated ketone) $cm^{-1}$; HRMS $M^+$ 234.1620 (calcd. for $C_{15}H_{22}O_2$: 234.1621). Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.87; H, 9.47; found: C, 76.83; H, 9.48.

### (1R, 6R, 7R, 10S)-(-)-7-(1-Formylethenyl)-10-hydroxy-4,10-dimethylbicyclo[4.4.0]dec-4-en-3-one (142) and (1R, 6R, 7R, 10S)-(-)-10-hydroxy-7-(1-hydroxymethylethenyl)-4,10-dimethylbicyclo[4.4.0]dec-4-en-3-one (143)



**142**



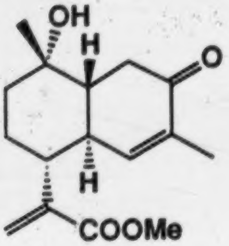
**143**

At 0°C, into a round bottom flask was introduced 183 mg (1.65 mmol, 0.8 eq) of selenium dioxide, 14 ml of dichloromethane (dried), 0.2 ml glacial acetic acid and 2.64 ml (7.92 mmol, 4 eq) of *tert*-butyl hydroperoxide (3 *M* solution in 2,2,4-trimethylpentane). Then 463.9 mg (1.98 mmol) of **141** in 4.8 ml of dichloromethane was added and the mixture was stirred at room temperature under an argon atmosphere for 98 h. Benzene (3 ml) was added and the solvent was removed on a rotary evaporator. Three ml of

1 *M* aqueous sodium hydroxide solution was then introduced and the aqueous layer was extracted with ether (4 x). The ether extracts were dried, filtered and concentrated. Flash chromatography of the residue with 20% ether in petroleum ether recovered starting material **141** (40.3 mg, 0.172 mmol). Further elution with 40, 60, 80 and 100% ether in petroleum ether gave **142** (125.2 mg, 0.5 mmol, 28% yield based on consumed starting material) as a white solid: $[\alpha]_D^{23}$ = -66.3° (c. 1.11, $CHCl_3$); mp 145-146°C (dichloromethane-petroleum ether); $^1H$ NMR (300 MHz, $CDCl_3$) δ 9.62 (s, 1H, CH**O**), 6.42 (s, 1H, C=C**H**H), 6.31 (m, 1H, C**H**=$CCH_3$), 6.23 (s, 1H, C=CH**H**), 2.79 (m, 1H, CHC**H**), 2.65 (dd, 1H, O=CC$\mathbf{H}_e$H, *J* = 16.5, 3.5 Hz), 2.50 (m, 1H, C**H**C=$CH_2$), 2.44 (dd, 1H, O=CCH$\mathbf{H}_{ax}$, *J* = 16.5, 14 Hz), 1.78 (m, 3H), 1.71 (dd, 3H, CH=CC$\mathbf{H}_3$, *J* = 2.5, 1.5 Hz), 1.60 (m, 2H), 1.45 (br s, 1H, O**H**), 1.24 (s, 3H, C$\mathbf{H}_3$); $^{13}C$ APT NMR (75 MHz, $CDCl_3$) δ 200.17 (C=O), 194.55 (CHO), 152.48 (=$CH_2$), 147.35 (=CH), 135.71, 135.34 (2 x =C), 69.66 (C-OH), 49.48 (2 x CH), 39.80 ($CH_2$), 39.41 (CH), 38.21, 28.61 (2 x $CH_2$), 27.75, 15.63 (2 x $CH_3$); FT-IR 3460 (OH), 1687, 1671 (C=O, conjugated) $cm^{-1}$; HRMS $M^+$ 248.1410 (calcd. for $C_{15}H_{20}O_3$: 248.1413). Continued elution with ether gave **143** (189.6 mg, 0.758 mmol, 42% yield based on consumed starting material) as a white solid: $[\alpha]_D^{23}$ = -60.9° (c. 0.89, $CHCl_3$); mp 122-123°C (dichloromethane-petroleum ether); $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.66 (m, 1H, C**H**=$CCH_3$), 5.27 (m, 1H, C=C**H**H), 5.04 (d, 1H, C=CH**H**, *J* = 1 Hz), 4.17 (br d, 2H, C$\mathbf{H}_2$OH, *J* = 5 Hz), 2.66 (m, 1H, CHC**H**), 2.63 (dd, 1H, O=CC$\mathbf{H}_e$H, *J* = 16, 3.5 Hz), 2.43 (dd, 1H, O=CCH$\mathbf{H}_{ax}$, *J* = 16, 14 Hz), 1.80 (m, 7H), 1.74 (dd, 3H, CH=CC$\mathbf{H}_3$, *J* = 2.5, 1.5 Hz), 1.54 (m, 1H), 1.22 (s, 3H, C$\mathbf{H}_3$); $^{13}C$ APT NMR (75 MHz,

$CDCl_3$) δ 200.44 (C=O), 150.57 (=C), 148.30 (=CH), 135.01 (=C), 111.45 (=$CH_2$), 69.93, 64.86 (2 x C-OH), 49.61, 45.94 (2 x CH), 40.06 ($CH_2$), 39.29 (CH), 38.29, 28.81 (2 x $CH_2$), 27.91, 15.67 (2 x $CH_3$); FT-IR 3400 (OH), 1659 (C=O, conjugated ketone) $cm^{-1}$; HRMS $M^+$ 250.1566 (calcd. for $C_{15}H_{22}O_3$: 250.1570).

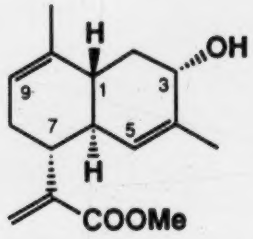
**(1R, 6S, 7R, 10S)-(-)-7-(1-Carbomethoxyethenyl)-10-hydroxy-4,10-dimethylbicyclo[4.4.0]dec-4-en-3-one (144)**



Compound **142** (186.6 mg, 0.752 mmol) was dissolved in 4 ml of acetone (distilled over potassium permanganate) and Jones reagent (1 ml) was added at room temperature. After 4 h, water was added to dissolve all the precipitate and the mixture was extracted with dichloromethane. The combined extracts were dried, filtered and concentrated to give the crude acid. Using the same procedure, 189.6 mg (0.758 mmol) of **143** in 4 ml of acetone was oxidized with Jones reagent.

Anhydrous potassium carbonate (492 mg, 3.55 mmol) was added to the above solution of acid in acetone (7 ml, distilled over potassium permanganate) at room temperature. The mixture was allowed to stir for 30 min and 0.31 ml (4.98 mmol) of methyl iodide was then added. After 26 h, 5% hydrochloric acid was added to dissolve the potassium carbonate. The acetone was removed under reduced pressure and the aqueous solution was extracted with dichloromethane. The extracts were dried, filtered and concentrated. Flash chromatography with 50-75% ether in petroleum ether gave **144** (247.2 mg, 0.889 mmol, 59% yield) as a colorless oil: $[\alpha]_D^{23}$ = -72.13° (c. 2.72, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 6.51 (m, 1H, $C\mathbf{H}{=}CCH_3$), 6.40 (s, 1H, $C{=}C\mathbf{H}H$), 5.70 (s, 1H, $C{=}CH\mathbf{H}$), 3.80 (s, 3H, $OC\mathbf{H}_3$), 2.78 (m, 1H, $CHC\mathbf{H}$), 2.65 (dd, 1H, $O{=}CC\mathbf{H}_eH$, $J$ = 16.5, 3.5 Hz), 2.44 (m, 2H, $O{=}CCH\mathbf{H}_{ax}$, $C\mathbf{H}C{=}CH_2$), 1.75 (m, 4H), 1.74 (dd, 3H, $CH{=}CC\mathbf{H}_3$, $J$ = 2.5, 1.5 Hz), 1.60 (m, 1H), 1.16 (s, 1H, $O\mathbf{H}$), 1.13 (s, 3H, $C\mathbf{H}_3$); $^{13}C$ APT NMR (75 MHz, $CDCl_3$) $\delta$ 200.20 (C=O), 167.55 (OC=O), 147.70 (CH=), 142.89 (=$CH_2$), 135.21 (=C), 125.68 (=C), 69.91 (C-OH), 52.13 ($OCH_3$), 49.59, 43.08, 39.62 (3 x CH), 39.99, 38.32, 29.13 (3 x $CH_2$), 27.86, 15.67 (2 x $CH_3$); FT-IR 3493 (OH), 1718 (C=O, conjugated ester), 1672 (C=O, conjugated ketone) $cm^{-1}$; HRMS $M^+$ 278.1516 (calcd. for $C_{16}H_{22}O_4$: 278.1519).

### (1R, 3S, 6S, 7R)-(-)-7-(1-Carbomethoxyethenyl)-4,10-dimethylbicyclo[4.4.0]dec-4,9-dien-3-ol (38)

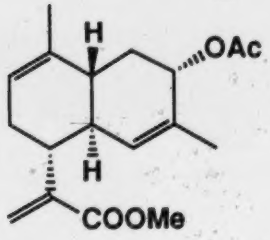


To a solution of ester **144** (9.8 mg, 0.035 mmol) in benzene was added 52.3 mg of CuSO$_4$-SiO$_2$ (1 mmol CuSO$_4$/g). The mixture was reflux for 8 h and then filtered and concentrated. Compound **145** showed the following signals: $^1$H NMR (300 MHz, CDCl$_3$) δ 6.64 (s, 1H, C**H**=C(CH$_3$)C=O), 6.39 (s, 1H, C=C**H**H), 5.65 (s, 1H, C=CH**H**), 5.44 (sharp m, 1H, C**H**=CCH$_3$), 3.79 (s, 3H, C**H**$_3$), 2.87 (dd, 1H, O=CC**H**H, *J* = 16.5, 3.5 Hz), 2.69 (m, 2H), 2.49 (m, 1H), 2.24 (m, 2H), 2.12 (dd, 1H, O=CCH**H**, *J* = 16.5, 14 Hz), 1.76 (dd, 3H, CH=CC**H**$_3$, *J* = 2.5, 1.5 Hz), 1.66 (dd, 3H, CHC=CC**H**$_3$, *J* = 1.5, 1.5 Hz). Compound **146** showed signals at δ 6.50 (sharp m, 1H), 6.40 (s, 1H), 5.70 (s, 1H). The mixture showed absorptions in FT-IR 1720 (C=O, conjugated ester), 1676 (C=O, conjugated ketone) cm$^{-1}$.

To a solution of the above enone in 1 ml of methanol, and 93.3 mg of CeCl$_3$·7H$_2$O was slowly added 8.8 mg of sodium borohydride at -78°C. After 6 h, the reaction was quenched with saturated ammonium chloride solution and extracted with dichloromethane. The organic extracts were dried, filtered and concentrated. Flash chromatography with 20% ether in petroleum ether gave **38** (4.0 mg, 0.015 mmol, 43% yield) as a colorless liquid: $[\alpha]_D^{23}$ = -77.35° (c. 0.49, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$) δ 6.30 (s, 1H, C=C**H**H), 5.54 (s, 1H, C=CH**H**), 5.38 (m, 2H, C**H**=CCH$_3$, CH$_3$C=C**H**), 4.20 (ddm, 1H, C**H**OH, *J* = 10, 6.5 Hz), 3.74 (s, 3H, OC**H**$_3$), 2.58 (ddd, 1H, C**H**C=CH$_2$, *J* = 11, 11, 5.5 Hz), 2.51 (ddd, 1H, HOCHC**H**H, *J* = 12, 6.5, 2 Hz), 2.37 (m, 1H, CHC**H**), 2.20 (m, 1H, C=CHC**H**H), 2.10 (m, 2H, C=CHCH**H**, C**H**C(CH$_3$)=CH), 1.70 (m, 3H, CH=CC**H**$_3$), 1.68 (br s, 3H,

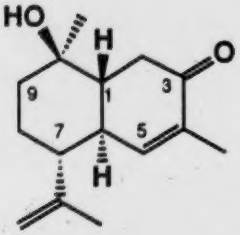
$CH_3C{=}CH$); 1.42 (m, 1H, OH), 1.27 (ddd, 1H, HOCHCH**H**, *J* = 12, 12, 10 Hz); FT-IR 1721 (C=O, conjugated ester) $cm^{-1}$; HRMS $M^+$ 262.1565 (calcd. for $C_{16}H_{22}O_3$: 262.1569).

### (1R, 5R, 6S, 9S)-9-Acetoxy-5-(1-carbomethoxyethenyl)-2,8-dimethylbicyclo[4.4.0]dec-2,7-diene (37)



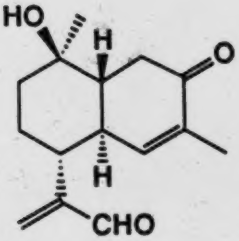
Pyridine (60 μl) and acetic anhydride (30 μl, 0.3 mmol) were added to alcohol **38** (3.2 mg, 0.012 mmol) at room temperature under an argon atmosphere. The reaction was stirred overnight and methanol (60 μl) was introduced. After 1 h, water was added and the mixture was extracted with ether. The ether extracts were washed with 1 *M* hydrochloric acid, saturated sodium chloride solution, dried, filtered and concentrated. Flash chromatography with 10% ether in petroleum ether gave a quantitative yield of **37**: $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.33 (br s, 1H, C=C**H**H), 5.58 (br s, 1H, C=CH**H**), 5.50 (m, 1H, C**H**=$CCH_3$), 5.45 (m, 1H, C**H**OAc), 5.39 (m, 1H, $CH_3C{=}C$**H**), 3.77 (s, 3H, $OCH_3$), 2.60 (m, 1H, C**H**C=$CH_2$), 2.56 (ddd, 1H, AcOCHC**H**H, *J* = 12, 7, 2 Hz), 2.40 (m, 1H, CHC**H**), 2.14 (m, 3H), 2.10 (s, 3H, $OCOCH_3$), 1.67 (br s, 3H, CH=$CCH_3$), 1.60 (br s, 3H, $CH_3C{=}CH$), 1.31 (ddd, 1H, AcOCHCH**H**, *J* = 13, 12, 10 Hz); FT-IR 1735 (C=O, saturated ester), 1723 (C=O, conjugated ester) cm$^{-1}$; CIMS 322 (M+NH$_4^+$), 305 (M+1); HRMS 244.1463 (M-CH$_3$COOH, C$_{16}$H$_{20}$O$_2$).

**(1R, 6R, 7R, 10R)-(-)-10-Hydroxy-4,10-dimethyl-7-(1-methylethenyl)bicyclo[4.4.0]dec-4-en-3-one (147)**



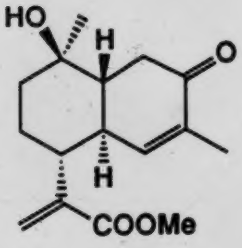
To a solution of **138** (164.0 mg, 0.529 mmol) in methanol-water (10 : 1, 13.2 ml) was added 1.319 g (5.69 mmol) of silver oxide. The mixture was refluxed for 20 h, cooled to room temperature and filtered through a layer of celite in a sintered funnel. The organic layer was then separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried, filtered and concentrated. Flash chromatography with 40-60% ether in petroleum ether gave **147** (78.7 mg, 0.336 mmol, 63% yield) as an oil: $[\alpha]_D^{23}$ = -53.15° (c. 3.9, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$) δ 6.57 (m, 1H, C**H**=CCH$_3$), 4.93 (m, 1H, C=CH**H**), 4.83 (br s, 1H, C=CH**H**), 2.79 (dd, 1H, O=CC**H**$_e$H, *J* = 16, 3 Hz), 2.20 (m, 1H), 2.16 (dd, 1H, O=CCH**H**$_{ax}$, *J* = 16, 14 Hz), 1.90 (m, 3H), 1.75 (dd, 3H, CH=CC**H**$_3$, *J* = 2, 1.5 Hz), 1.72 (dd, 3H, C**H**$_3$C=CH$_2$, *J* = 1.5, 1 Hz), 1.70 (m, 1H), 1.53 (m, 3H), 1.23 (s, 3H, CH$_3$); $^{13}$C APT NMR (75 MHz, CDCl$_3$) δ 200.09 (C=O), 147.06 (=CH), 146.24, 135.30 (2 x =C), 113.22 (=CH$_2$), 71.21 (C-OH), 50.73, 49.79, 41.60 (3 x CH), 41.60, 38.15, 29.43 (3 x $CH_2$), 21.09, 19.24, 15.70 (3 x $CH_3$); FT-IR 3440 (OH), 1675 (C=O, conjugated ketone) $cm^{-1}$; HRMS $M^+$ 234.1623 (calcd. for $C_{15}H_{22}O_2$: 234.1621).

### (1R, 6R, 7R, 10R)-(-)-7-(1-Formylethenyl)-10-hydroxy-4,10-dimethylbicyclo[4.4.0]dec-4-en-3-one (148)



To a solution of **147** (31.6 mg, 0.135 mmol) in acetic acid (1.5 ml) was added 64.4 mg (0.58 mmol) of selenium dioxide. The mixture was warmed up to 70°C over 15 min. Then benzene was added and the acetic acid was evaporated under reduced pressure. Repeated flash chromatography with 40% ethyl acetate in petroleum ether gave **148** (14.6 mg, 0.059 mmol, 44% yield) as a very light yellow oil: $[\alpha]_D^{23} = -70.90°$ (c. 0.646, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) δ 9.62 (s, 1H, C**H**O), 6.38 (s, 1H, C=C**H**H), 6.27 (m, 1H, C**H**=$CCH_3$), 6.23 (s, 1H, C=CH**H**), 2.81 (dd, 1H, O=$CC\mathbf{H}_eH$, *J* = 16, 3 Hz), 2.68 (m, 1H), 2.44 (m, 1H), 2.18 (dd, 1H, O=$CCH\mathbf{H}_{ax}$, *J* = 16, 14 Hz), 1.89 (m, 2H), 1.75 (m, 1H), 1.73 (dd, 3H, CH=$CC\mathbf{H}_3$, *J* = 2.5, 1.5 Hz), 1.60 (m, 3H), 1.27 (s, 3H, $C\mathbf{H}_3$); $^{13}C$ APT NMR (75 MHz, $CDCl_3$) δ 199.70 (C=O), 194.30 (CHO), 151.72 (=$CH_2$), 145.93 (=CH), 136.14, 135.74 (2 x =C), 71.07 (C-OH), 50.95 (2 x CH), 41.62 ($CH_2$), 41.10 (CH), 38.03, 30.00 (2 x $CH_2$), 21.03, 15.69 (2 x $CH_3$); FT-IR 3460 (OH), 1675 (C=O, conjugated) $cm^{-1}$; HRMS $M^+$ 248.1414 (calcd. for $C_{15}H_{20}O_3$: 248.1413).

### (1R, 6R, 7R, 10R)-(-)-7-(1-Carbomethoxyethenyl)-10-hydroxy-4,10-dimethyl-bicyclo-[4.4.0]dec-4-en-3-one (149)

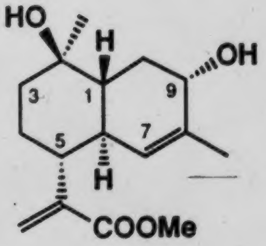


Jones reagent (0.15 ml) was added to a solution of **148** (18.5 mg, 0.0746 mmol) in acetone (1.5 ml, distilled from potassium permanganate) at room temperature. After stirring for 4.5 h, water was added and the mixture was extracted with dichloromethane. The combined extracts were dried, filtered and concentrated to give the crude acid.

Anhydrous potassium carbonate (27.3 mg, 0.198 mmol) was added to a solution of the above acid in acetone (1.5 ml, distilled over potassium permanganate) at room temperature. The mixture was allowed to stir for 30 min and 15 µl (0.246 mmol) of methyl iodide was then added. After 17 h, 5% hydrochloric acid was added to dissolve the potassium carbonate. Then the acetone was removed under reduced pressure and the aqueous solution was extracted with dichloromethane. The extracts were dried, filtered and concentrated. Flash chromatography with 35% ethyl acetate in

petroleum ether gave **149** (7 mg, 0.025 mmol, 34% yield): $[\alpha]_D^{22}$ = -78° (c. 0.7, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.43 (m, 1H, $C\mathbf{H}{=}CCH_3$), 6.38 (s, 1H, $C{=}C\mathbf{H}H$), 5.67 (s, 1H, $C{=}CH\mathbf{H}$), 3.80 (s, 3H, $OC\mathbf{H}_3$), 2.80 (dd, 1H, $O{=}CC\mathbf{H}_eH$, *J* = 16, 3 Hz), 2.59 (m, 1H, $CHC\mathbf{H}$), 2.38 (ddd, 1H, $C\mathbf{H}C{=}CH_2$, *J* = 11.5, 11.5, 4 Hz), 2.18 (dd, 1H, $O{=}CCH\mathbf{H}_{ax}$, *J* = 16, 14 Hz), 1.86 (m, 3H), 1.74 (dd, 3H, $CH{=}CC\mathbf{H}_3$, *J* = 2.5, 1.5 Hz), 1.62 (m, 2H), 1.45 (br s, 1H), 1.25 (s, 3H, $C\mathbf{H}_3$); $^{13}C$ APT NMR (75 MHz, $CDCl_3$) δ 199.89 (C=O), 167.09 (OC=O), 146.49 (=CH), 142.12 (=C), 135.52 (=C), 126.46 ($=CH_2$), 71.18 (C-OH), 52.11 ($OCH_3$), 50.98, 44.71 (2 x CH), 41.70 ($CH_2$), 41.33 (CH), 38.11, 30.45 (2 x $CH_2$), 21.08, 15.74 (2 x $CH_3$); FT-IR 3460 (OH), 1717 (C=O, conjugated ester), 1674 (C=O, conjugated ketone) $cm^{-1}$; HRMS $M^+$ 278.1520 (calcd. for $C_{16}H_{22}O_4$: 278.1519).

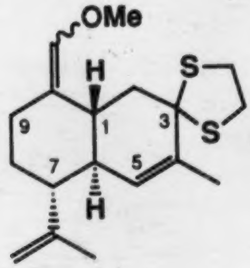
### (1R, 2R, 5R, 6S, 9S)-(-)-5-(1-Carbomethoxyethenyl)-2,8-dimethylbicyclo[4.4.0]dec-7-en-2,9-diol (34)



At -78°C, to a solution of enone **149** (6.5 mg, 0.0234 mmol) in 0.5 ml methanol and 74.5 mg (0.2 mmol) of cerium(III) chloride heptahydrate was slowly added 6.8 mg (0.18 mmol) of sodium borohydride. After 1.3 h, the reaction was quenched with saturated ammonium chloride solution and extracted with dichloromethane. The organic extracts were dried, filtered and concentrated. Flash chromatography with 40% ethyl acetate in petroleum ether gave **34** (5.6 mg, 0.02 mmol, 85% yield) as a white solid: $[\alpha]_D^{22}$ = -97.5° (c. 0.44, EtOH); mp 185-186°C (acetone); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.30 (d, 1H, C=C**H**H, $J$ = 1 Hz), 5.57 (br s, 1H, C=CH**H**), 5.23 (m, 1H, C**H**=CCH$_3$), 4.20 (m, 1H, C**H**OH), 3.77 (s, 3H, OCH$_3$), 2.40 (ddd, 1H, CHOHCH**H**, $J$ = 12, 6, 2 Hz), 2.23 (m, 2H, C**H**C=CH$_2$, C**H**CH), 1.77 (m, 2H, O**H**, CH$_2$CH**H**), 1.70 (br s, 3H, CH=CCH$_3$), 1.22-1.56 (m, 6H, ), 1.21 (s, 3H, CH$_3$); $^{13}$C APT NMR (75 MHz, CDCl$_3$) $\delta$ 167.52 (OC=O), 142.98 (=CH$_2$), 137.48 (C=), 126.52 (CH=), 125.51 (C=), 71.54, 71.50 (2 x C-OH), 51.93 (OCH$_3$), 49.27, 45.10 (2 x CH), 42.03 (CH$_2$), 41.20 (CH), 33.10, 31.19 (2 x CH$_2$), 20.91, 19.00 (2 x CH$_3$); FT-IR 3328 (OH), 1716 (C=O, conjugated ester) cm$^{-1}$; HRMS M$^+$ 280.1667 (calcd. for $C_{16}H_{24}O_4$: 280.1675).

## IV. STUDIES TOWARDS THE TOTAL SYNTHESIS OF (+)-ARTEMISININ

### (1R, 6S, 7R)-3,3-Ethylenedithio-10-methoxymethylene-4-methyl-7-(1-methylethenyl)bicyclo[4.4.0]dec-4-ene (150)

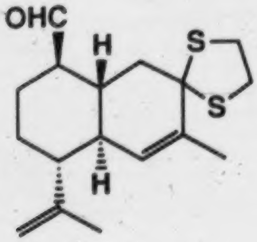


Potassium hydride (390.8 mg, 35% by wt, 3.42 mmol) contained in a 3-necked flask was washed with benzene (dried, 3 x) under an argon atmosphere. To this was added 1.50 ml of dried DMSO *via* a syringe and the mixture was stirred at room temperature until the evolution of hydrogen had ceased. Methoxymethyltriphenylphosphonium bromide (1.2262 g, 3.58 mmol) in 5 ml of DMSO was then added to the light greenish yellow solution. The resulting dark red solution was stirred at room temperature for 10 min before use.

Ketone **79** (199.2 mg, 0.677 mmol) in 1.5 ml of benzene was added to the above solution of methoxymethylenetriphenylphosphorane, the color of the solution remained dark red. The mixture was stirred at room temperature for 21 h and water was then added. The mixture was extracted with ether and the extracts were washed with water, dried, filtered and concentrated. Flash chromatography with petroleum ether removed the undesired triphenylphosphine. Elution with 1% ether in petroleum ether gave a mixture of **150** (199.8 mg, 0.620 mmol) in a ratio of 88 : 12 (from $^1$H NMR integration) in 92% yield. The major compound showed $^1$H nmr signals at $\delta$ 5.68 (br s, 1H, $C{=}CHOCH_3$), 5.43 (m, 1H, $CH{=}CCH_3$), 4.80 (m, 1H, $C{=}CHH$), 4.74 (br s, 1H, $C{=}CHH$), 3.58 (s, 3H, $OCH_3$), 3.34 (m, 4H, $SCH_2CH_2S$), 2.89 (m, 1H), 2.46 (d, 1H, $J = 11.5$ Hz), 1.95 (dd, 3H, $CH{=}CCH_3$, $J = 1.5$, 1 Hz), 1.63 (br s, 3H, $CH_3C{=}CH_2$). The minor compound showed signals at $\delta$ 5.76 (br s, 1H, $C{=}CHOCH_3$), 5.39 (br s, 1H, $CH{=}CCH_3$), 3.49 (s, 3H, $OCH_3$), 3.34 (m, 4H, $SCH_2CH_2S$), 1.97 (br s, 3H,

$CH=CCH_3$), 1.64 ( br s, 3H, $CH_3C=CH_2$). The mixture showed the following spectral data: FT-IR 1685, 1644 (C=C) $cm^{-1}$; HRMS $M^+$ 322.1423 (calcd. for $C_{18}H_{26}OS_2$: 322.1425).

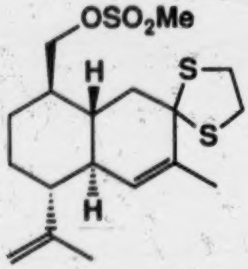
### (1R, 6R, 7R, 10R)-3,3-Ethylenedithio-10-formyl-4-methyl-7-(1-methylethenyl)bicyclo[4.4.0]dec-4-ene (151)



A solution of enol ether **150** (1.03 g, 3.2 mmol) containing *p*-toluenesulfonic acid (0.122 g, 0.64 mmol) in 36 ml of acetone-water (5 : 1) was refluxed for 10 h. The solvent was then removed under reduced pressure and the residue was dissolved in ether (40 ml). The ethereal solution was washed with 1 *M* aqueous sodium hydroxide solution, dried, filtered and concentrated to give a mixture of aldehyde in the ratio of 35 : 65 from ($^1$H NMR integration). The minor compound proved to be the desired product.

The mixture of aldehydes was dissolved in 36.5 ml of methanol and 7.3 ml of 1 *M* aqueous sodium hydroxide solution was added. The mixture was stirred at room temperature for 24 h. The mixture was then extracted with dichloromethane (3 x 20 ml) and the extracts were washed with saturated aqueous sodium chloride solution, dried, filtered and concentrated. Flash chromatography with 5% ether in petroleum ether gave the desired major product **151** (909.8 mg, 2.95 mmol, 92% yield, 93 : 7 from $^1$H NMR integration) as a white solid: $^1$H NMR (300 MHz, $CDCl_3$) δ 9.58 (d, 1H, CHO, *J* = 4 Hz), 5.43 (m, 1H, C**H**=$CCH_3$), 4.83 (m, 1H, C=CH**H**), 4.74 (br s, 1H, C=CH**H**), 3.29 (m, 4H, $SCH_2CH_2S$), 2.35 (dd, 1H, $S_2CCHH$, *J* = 13, 1 Hz), 2.06 (m, 2H), 1.93 (br s, 3H, CH=$CCH_3$), 1.82 (m, 5H), 1.65 (br s, 3H, $CH_3C$=$CH_2$), 1.50 (m, 3H); $^{13}$C APT NMR (75 MHz, $CDCl_3$) δ 204.61 (CHO), 146.82, 136.05 (2 x =C), 128.20 (=CH), 112.65 (=$CH_2$), 69.48 ($S_2C$), 53.97, 49.48 (2 x CH), 48.63 ($CH_2$), 41.96 (CH), 41.35, 40.25 (2 x $CH_2$), 39.44 (CH), 30.69, 26.07 (2 x $CH_2$), 19.76, 19.08 (2 x $CH_3$); FT-IR 1725 (CHO) cm$^{-1}$; HRMS M$^+$ 308.1269 (calcd. for $C_{17}H_{24}OS_2$: 308.1270). Anal. Calcd. for $C_{17}H_{24}OS_2$: C, 66.21; H, 7.85; S, 20.75; found: C, 66.14; H, 8.03; S, 20.71.

**(1S, 6R, 7R, 10S)-(-)-3,3-Ethylenedithio-10-methanesulfonyloxymethyl-4-methyl-7-(1-methylethenyl)bicyclo[4.4.0]dec-4-ene (153)**



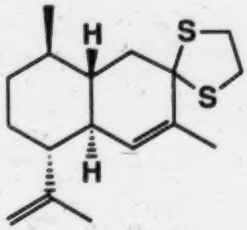
To a suspension of lithium aluminium hydride (336.5 mg, 8.86 mmol, 2.5 eq) in 16 ml of tetrahydrofuran (dried) was added a solution of aldehyde **151**

(1.076 g, 3.49 mmol) in 10 ml tetrahydrofuran under an argon atmosphere. The mixture was refluxed for 0.5 h and allowed to cool to room temperature. The excess hydride was destroyed by the addition of ethyl acetate and 1 *M* hydrochloric acid. The mixture was then extracted with ether (3 x 20 ml) and the combined extracts were dried, filtered and concentrated to give the alcohol as a white solid: $^1$H NMR (300 MHz, $CDCl_3$) δ 5.43 (br s, 1H, C**H**=$CCH_3$), 4.81 (m, 1H, C=C**H**H), 4.73 (dd, 1H, C=CH**H**, *J* = 1.5, 1 Hz), 3.70 (m, 2H, C**H**$_2$OH), 3.32 (m, 4H, SC**H**$_2$C**H**$_2$S), 2.57 (dd, 1H, $S_2$CC**HH**, *J* = 13, 1.5 Hz), 1.93 (dd, 3H, CH=CC**H**$_3$, *J* = 1.5, 1 Hz), 1.65 (dd, 3H, C**H**$_3$C=$CH_2$, *J* = 1.5, 1 Hz); FT-IR 3360 (OH) cm$^{-1}$; HRMS M$^+$ 310.1425 (calcd. for $C_{17}H_{26}OS_2$: 310.1425).

Methanesulfonyl chloride, 0.6 ml (7.68 mmol) and 1.21 ml (8.72 mmol) of triethylamine were added to a solution of the above alcohol in 23 ml of dichloromethane at 0°C under an argon atmosphere. After 40 min, 5 ml of 1 *M* hydrochloric acid was added. The organic layer was separated and the aqueous layer extracted with ether (2 x 5 ml). The combined organic extracts were dried, filtered and concentrated. Flash chromatography of the residue on silica gel with 25% ether in petroleum ether gave **153** (1.24 g, 3.2 mmol, 92% yield in the ratio of 95 : 5 from $^1$H NMR integration) as a white solid. Recrystallization from dichloromethane-petroleum ether gave pure **153**: $[\alpha]_D^{23}$ = -31.88° (c. 1.38, $CHCl_3$); mp 119-120°C (dichloromethane-petroleum ether); $^1$H NMR (400 MHz, $CDCl_3$) δ 5.42 (br s, 1H, C**H**=$CCH_3$), 4.83 (m, 1H, C=C**H**H), 4.74 (br s, 1H, C=CH**H**), 4.28 (dd, 1H, C**H**HOSO$_2$CH$_3$, *J* = 10, 3.5 Hz), 4.23 (dd, 1H, CH**H**OSO$_2$CH$_3$,

$J$ = 10, 6 Hz), 3.33 (m, 4H, $SCH_2CH_2S$), 3.06 (s, 3H, $OSO_2CH_3$), 2.52 (dd, 1H, $S_2CCHH$, $J$ = 13.5, 2 Hz), 1.94 (m, 2H), 1.92 (br s, 3H, $CH{=}CCH_3$), 1.81 (m, 2H), 1.74 (m, 1H), 1.66 (s, 3H, $CH_3C{=}CH_2$), 1.61 (m, 1H), 1.43 (m, 3H); $^{13}C$ APT NMR (75 MHz, $CDCl_3$) δ 147.24 (p), 135.48 (p), 128.71 (a), 112.36 (p), 71.18 (p), 69.87 (p), 49.87 (a), 47.22 (p), 42.81 (a), 41.37 (p), 41.05 (a), 40.13 (p), 40.10 (a), 37.48 (a), 31.60 (p), 29.45 (p), 19.68 (a), 19.05 (a); FT-IR 1640 (C=C) $cm^{-1}$; HRMS $M^+$ 388.1193 (calcd. for $C_{18}H_{28}O_3S_3$: 388.1200). Anal. Calcd. for $C_{18}H_{28}O_3S_3$: C, 55.65; H, 7.27; S, 24.71; found: C, 55.81; H, 7.40; S, 24.24.

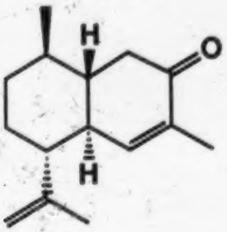
### (1S, 6R, 7R, 10R)-(-)-3,3-Ethylenedithio-4,10-dimethyl-7-(1-methylethenyl)bicyclo[4.4.0]dec-4-ene (154)



To a suspension of lithium aluminium hydride (380.4 mg, 10 mmol, 3.1 eq) in 16 ml of dried tetrahydrofuran was added a solution of **153** (1.24 g, 3.2 mmol) also in 8 ml of dried tetrahydrofuran under an argon atmosphere. The mixture was refluxed for 1 h and allowed to cool to room temperature. Excess hydride was destroyed by the addition of ethyl acetate and 1 *M* hydrochloric acid. The mixture was then extracted with ether (3 x 20 ml) and the combined extracts were dried, filtered and concentrated. Flash chromatography with petroleum ether gave **154** (862.6 mg, 2.93 mmol, 91%

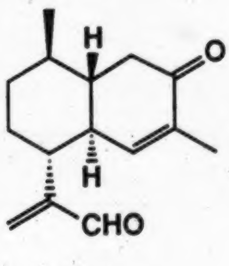
yield) as a colorless liquid: $[\alpha]_D^{23}$ = -29.17° (c. 0.84, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.40 (m, 1H, CH=$CCH_3$), 4.80 (m, 1H, C=CH**H**), 4.72 (br s, 1H, C=CH**H**), 3.33 (m, 4H, $SCH_2CH_2S$), 2.58 (dd, 1H, $S_2CCHH$, *J* = 18, 2 Hz), 1.93 (dd, 3H, CH=$CCH_3$, *J* = 2.5, 1 Hz), 1.73 (m, 5H), 1.65 (br s, 3H, $CH_3C$=$CH_2$), 1.41 (m, 1H), 1.17 (m, 3H), 0.95 (d, 3H, $CHCH_3$, *J* = 6 Hz); $^{13}C$ APT NMR (75 MHz, $CDCl_3$) δ 148.08, 135.42 (2 x C=), 129.40 (CH=), 111.81 ($CH_2$=), 70.41 ($S_2C$), 50.43 (CH), 48.03 ($CH_2$), 46.48, 43.08 (2 x CH), 41.35, 40.32 (2 x $CH_2$), 35.51 (CH), 35.41, 32.47 (2 x $CH_2$), 19.76, 19.32, 19.12 (3 x $CH_3$); FT-IR 1646 (C=C) $cm^{-1}$; HRMS $M^+$ 294.1476 (calcd. for $C_{17}H_{26}S_2$: 294.1476). Anal. Calcd. for $C_{17}H_{26}S_2$: C, 69.35; H, 8.91; S, 21.74; found: C, 69.31; H, 8.99; S, 21.99.

### (1S, 6R, 7R, 10R)-(-)-4,10-Dimethyl-7-(1-methylethenyl)bicyclo-[4.4.0]dec-4-en-3-one (155)

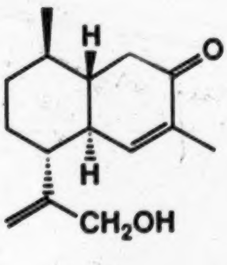


To a solution of thioacetal **154** (295.9 mg, 1 mmol) in 17 ml of 80% aqueous acetonitrile was added a mercury(II) chloride solution (823.7 mg, 3 mmol in 5 ml of 80% aqueous acetonitrile). After stirring at room temperature for 16 h, the mixture was filtered through a layer of silica gel in a sintered funnel. The filtrate was concentrated and the residue was dissolved in dichloromethane. The dichloromethane layer was washed with water (3 x), dried, filtered and concentrated. Flash chromatography on silica gel using 2% ether in petroleum ether as the eluant gave **155** (193.7 mg, 0.89 mmol, 89% yield) as a viscous oil: $[\alpha]_D^{23}$ = -69.44° (c. 1.26, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$) δ 6.63 (m, 1H, C**H**=CCH$_3$), 4.89 (m, 1H, C=C**H**H), 4.80 (br s, 1H, C=CH**H**), 2.76 (dd, 1H, O=CC**H**H, *J* = 17, 3 Hz), 2.06 (m, 1H, CHC**H**), 2.02 (dd, 1H, O=CCH**H**, *J* = 17, 13 Hz), 1.92 (ddd, 1H, C**H**C(CH$_3$)=CH$_2$, *J* = 12, 12, 3.5 Hz), 1.75 (dd, 3H, CH=CC**H**$_3$, *J* = 2.5, 1.5 Hz), 1.73 (m, 2H), 1.70 (dd, 3H, C**H**$_3$C=CH$_2$, *J* = 1.5, 1 Hz), 1.43 (m, 3H), 1.12 (m, 1H), 0.91 (d, 3H, CHC**H**$_3$, *J* = 6 Hz); $^{13}$C APT NMR (75 MHz, CDCl$_3$) δ 200.34 (C=O), 148.53 (=CH), 147.20, 135.26 (2 x =C), 112.69 (=CH$_2$), 49.84, 47.82, 43.41 (3 x CH), 42.81 (CH$_2$), 36.80 (CH), 34.83, 32.23 (2 x CH$_2$), 19.19, 19.11, 15.69 (3 x CH$_3$); FT-IR 1677 (C=O), 1647 (C=C) cm$^{-1}$; HRMS M$^+$ 218.1668 (calcd. for $C_{15}H_{22}O$: 218.1670). Anal. Calcd. for $C_{15}H_{22}O$: C, 82.51; H, 10.16; found: C, 82.39; H, 9.95.

### (1S, 6R, 7R, 10R)-(-)-7-(1-Formylethenyl)-4,10-dimethylbicyclo-[4.4.0]dec-4-en-3-one (156) and (1S, 6R, 7R, 10R)-(-)-7-(1-hydroxymethylethenyl)-4,10-dimethylbicyclo[4.4.0]dec-4-en-3-one (157)



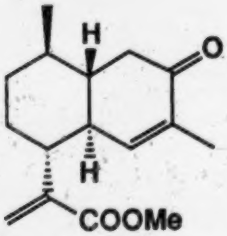
**156**



**157**

Into a round bottom flask was introduced 98.4 mg (0.887 mmol, 1 eq) of selenium dioxide, 7 ml of dichloromethane (dried), 0.1 ml glacial acetic acid and 1.19 ml (3.56 mmol, 4 eq) of *tert*-butyl hydroperoxide (3 *M* solution in 2,2,4-trimethylpentane) at 0°C. To this was added 193.7 mg (0.89 mmol) of **155** in 2 ml of dichloromethane and the mixture was stirred at room temperature under an argon atmosphere for 6 days. Benzene (3 ml) was then added and the solvent was removed on a rotary evaporator. A quantity of 3 ml of 1 *M* aqueous sodium hydroxide solution was then introduced and the aqueous layer was extracted with ether (4 x 5ml). The ether extracts were dried, filtered and concentrated. Flash chromatography of the residue with 15% ether in petroleum ether gave compound **156** (92.4 mg, 0.398 mmol, 45% yield) as a colorless oil: $[\alpha]_D^{22}$ = -99.63° (c. 1.08, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 9.62 (s, 1H, C**H**O), 6.35 (s, 1H, C=C**H**H), 6.32 (m, 1H, C**H**=$CCH_3$), 6.20 (s, 1H, C=CH**H**), 2.79 (dd, 1H, O=CC**H**H, $J$ = 16.5, 3.5 Hz), 2.50 (ddd, 1H, $CH_2C$**H**, $J$ = 12, 12, 3 Hz), 2.06 (dd, 1H, O=CCH**H**, $J$ = 16.5, 13 Hz), 1.78 (m, 2H), 1.72 (dd, 3H, CH=$CC$**H**$_3$, $J$ = 2.5, 1.5 Hz), 1.46 (m, 3H), 1.20 (m, 1H), 0.92 (d, 3H, CHC**H**$_3$, $J$ = 6.5 Hz); $^{13}C$ APT NMR (75 MHz, $CDCl_3$) $\delta$ 199.87 (C=O), 194.46 (CHO), 152.68 (=$CH_2$), 147.17 (=CH), 135.73, 135.51 (2 x =C), 47.94, 44.33 (2 x CH), 42.60 ($CH_2$), 36.58 (CH), 34.79, 33.31 (2 x $CH_2$), 19.00, 15.65 (2 x $CH_3$); FT-IR 1688, 1674 (conjugated C=O) $cm^{-1}$; HRMS $M^+$ 232.1461 (calcd. for $C_{15}H_{20}O_2$: 232.1463). Further elution with 25% ether in petroleum ether gave compound **157** (59.1 mg, 0.252 mmol, 28% yield) as a colorless oil: $[\alpha]_D^{23}$ = -105.59° (c. 3.94, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 6.64 (m, 1H, C**H**=CCH$_3$), 5.26 (m, 1H, C=CH**H**), 4.89 (br s, 1H, C=CH**H**), 4.15 (br s, 2H, C**H**$_2$OH), 2.76 (dd, 1H, O=CCH**H**, *J* = 16, 3 Hz), 2.20 (m, 1H, CHC**H**), 2.04 (dd, 1H, O=CCH**H**, *J* = 16, 13 Hz), 1.85 (m, 3H), 1.74 (dd, 3H, CH=CC**H**$_3$, *J* = 2.5, 1.5 Hz), 1.66 (m, 1H), 1.41 (m, 3H), 1.12 (m, 1H), 0.90 (d, 3H, CHC**H**$_3$, *J* = 6 Hz); $^{13}$C APT NMR (75 MHz, CDCl$_3$) δ 200.43 (C=O), 151.18 (=C), 148.17 (=CH), 135.68 (=C), 110.92 (=CH$_2$), 64.98 (CH$_2$OH), 48.08, 45.89, 44.48 (3 x CH), 42.70 (CH$_2$), 36.68 (CH), 35.07, 33.80 (2 x CH$_2$), 19.07, 15.70 (2 x CH$_3$); FT-IR 3452 (OH), 1672 (conjugated C=O) cm$^{-1}$; HRMS M$^+$ 234.1621 (calcd. C$_{15}$H$_{22}$O$_2$: 234.1620).

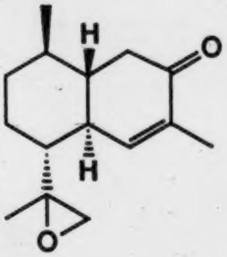
**(1S, 6S, 7R, 10R)-(-)-7-(1-Carbomethoxyethenyl)-4,10-dimethylbicyclo[4.4.0]dec-4-en-3-one (158)**



Jones reagent (1 ml) was added to a solution of **156** (68.2 mg, 0.294 mmol) and **157** (39.4 mg, 0.168 mmol) in acetone (6 ml, distilled from potassium permanganate) at room temperature. After stirring for 16 h, water was added and the mixture was extracted with dichloromethane. The combined extracts were dried, filtered and concentrated to give the crude acid.

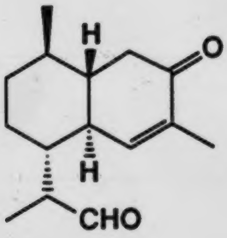
Anhydrous potassium carbonate (131.1 mg, 0.95 mmol) was added to a solution of the above acid in acetone (6 ml, distilled over potassium permanganate) at room temperature. The mixture was allowed to stir for 30 min and 95 µl (1.52 mmol) of methyl iodide was then added. After 21 h, 5% dilute hydrochloric acid was added to dissolve the potassium carbonate. The acetone was then removed under reduced pressure and the aqueous solution extracted with dichloromethane. The extracts were dried, filtered and concentrated. Flash chromatography with 15% ether in petroleum ether gave **158** (59.0 mg, 0.225 mmol, 49% yield) as a colorless oil: $[\alpha]_D^{22}$ = -102.5° (c. 2.76, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 6.50 (br s, 1H, $C\mathbf{H}{=}CCH_3$), 6.36 (s, 1H, $C{=}C\mathbf{H}H$), 5.62 (s, 1H, $C{=}CH\mathbf{H}$), 3.80 (s, 3H, $OC\mathbf{H}_3$), 2.77 (dd, 1H, $O{=}CC\mathbf{H}H$, $J$ = 17, 3 Hz), 2.44 (m, 1H, $CH_2C\mathbf{H}$), 2.38 (m, 1H, $CHC\mathbf{H}$), 2.05 (dd, 1H, $O{=}CCH\mathbf{H}$, $J$ = 17, 13.5 Hz), 1.86 (dddd, 1H, $CH_2C\mathbf{H}H$, $J$ = 13, 3.5, 3.5, 3.5 Hz), 1.77 (m, 1H, $H_3CCHC\mathbf{H}H$), 1.73 (br s, 3H, $CH{=}CC\mathbf{H}_3$), 1.45 (m, 3H, $CHC\mathbf{H}CH_3$, $CH_2CH\mathbf{H}$, $C\mathbf{H}CH_3$), 1.19 (dddd, 1H, $H_3CCHCH\mathbf{H}$, $J$ = 13, 13, 11.5, 4 Hz), 0.92 (d, 3H, $CHC\mathbf{H}_3$, $J$ = 6 Hz); $^{13}C$ APT NMR (75 MHz, $CDCl_3$) $\delta$ 200.08 (C=O), 167.73 (OC=O), 147.74 (=CH), 143.18 (=C), 135.53 (=C), 125.70 (=$CH_2$), 52.04 ($OCH_3$), 48.05, 44.59, 43.75 (3 x CH), 42.70 ($CH_2$), 36.62 (CH), 34.94, 33.84 (2 x $CH_2$), 19.04, 15.69 (2 x $CH_3$); FT-IR 1720 (C=O, conjugated ester), 1676 (C=O, conjugated ketone) $cm^{-1}$; HRMS $M^+$ 262.1565 (calcd. for $C_{26}H_{22}O_3$: 262.1569).

**(1S, 6S, 7R, 10R)-4,10-Dimethyl-7-(1-methylepoxyethyl)bicyclo-[4.4.0]dec-4-en-3-one (159).**



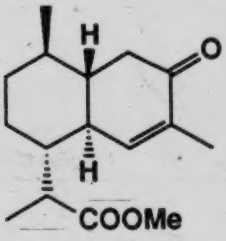
A solution of **155** (35 mg, 0.16 mmol) in 1.5 ml of dichloromethane (dried) was treated with 46.9 mg (0.22 mmol, 80% by wt) of 3-chloroperoxybenzoic acid and stirred at 0°C for 10 h. More dichloromethane was added and the solution was washed twice with saturated aqueous sodium bicarbonate. The aqueous layer was re-extracted with dichloromethane and the combined organic extracts were washed with saturated aqueous sodium chloride solution, dried, filtered and concentrated. Flash chromatography with 16% ether in petroleum ether gave **159** (34 mg, 0.145 mmol, 91% yield). The $^1$H NMR (300 MHz, $CDCl_3$) spectrum showed two sets of signals in an integral ratio of 1 : 1.7. The major compound showed signals at δ 6.78 (m, 1H, C**H**=$CCH_3$), 2.81 (m, 2H), 2.74 (m, 2H), 1.79 (dd, 3H, CH=CC**H**$_3$, $J$ = 2.5, 1.5 Hz), 1.29 (s, 3H, C**H**$_3$), 0.90 (d, 3H, CHC**H**$_3$, $J$ = 6 Hz). The minor compound showed signals at δ 7.14 (m, 1H, C**H**=$CCH_3$), 2.60 (d, 1H, OC**H**H, $J$ = 5 Hz), 2.49 (d, 1H, OCH**H**, $J$ = 5 Hz), 2.17 (m, 1H), 1.80 (dd, 3H, CH=CC**H**$_3$, $J$ = 2.5, 1.5 Hz), 1.31 (s, 3H, C**H**$_3$), 0.90 (d, 3H, CHC**H**$_3$, $J$ = 6 Hz). The mixture also showed the following spectral data: FT-IR 1675 (C=O, conjugated) cm$^{-1}$; HRMS M$^+$ 234.1618 (calcd. for $C_{15}H_{22}O_2$: 234.1620). Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.87; H, 9.47; found: C, 76.66; H, 9.24.

### (1S, 6R, 7R, 10R)-7-(1-Formylethyl)-4,10-dimethylbicyclo[4.4.0]-dec-4-en-3-one (160)



To a solution of **159** (269.0 mg, 1.15 mmol) in dichloromethane at 0°C, was added a solution of boron trifluoride etherate (0.14 ml, 1.15 mmol). After 10 min, 1 ml of $H_2O$ was added and the layers separated. The aqueous layer was extracted with dichloromethane (2 x 5 ml) and the combined organic extracts were dried, filtered and concentrated. Flash chromatography of the residue on silica gel eluted with 10% ether in petroleum ether gave compound **160** (218.2 mg, 0.932 mmol) in 81% yield. The $^1$H NMR (300 MHz, $CDCl_3$) spectrum showed two sets of signals in an integral ratio of 1 : 2.2. The major compound showed signals at $\delta$ 9.71 (s, 1H, CH**O**), 6.72 (br s, 1H, C**H**=$CCH_3$), 1.80 (dd, 3H, CH=$CC\mathbf{H}_3$, $J$ = 2.5, 1.5 Hz), 1.07 (d, 3H, $\mathbf{H}_3$CCHCHO, $J$ = 7 Hz), 0.90 (d, 3H, $CHC\mathbf{H}_3$, $J$ = 6.5 Hz). The minor compound showed signals at $\delta$ 9.84 (d, 1H, CH**O**, $J$ = 1 Hz), 6.60 (m, 1H, C**H**=$CCH_3$), 1.76 (dd, 3H, CH=$CC\mathbf{H}_3$, $J$ = 2.5, 1.5 Hz), 1.20 (d, 3H, $\mathbf{H}_3$CCHCHO, $J$ = 7 Hz), 0.90 (d, 3H, $CHC\mathbf{H}_3$, $J$ = 6.5 Hz). The mixture also showed the following spectral data: FT-IR 1721 (CHO), 1674 (C=O, conjugated) cm$^{-1}$; HRMS M$^+$ 234.1620 (calcd. for $C_{15}H_{22}O_2$: 234.1620).

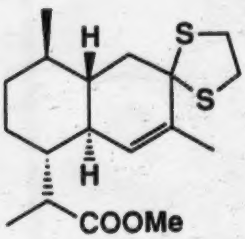
### (1S, 6R, 7R, 10R)-7-(1-Carbomethoxyethyl)-4,10-dimethylbicyclo[4.4.0]dec-4-en-3-one (161)



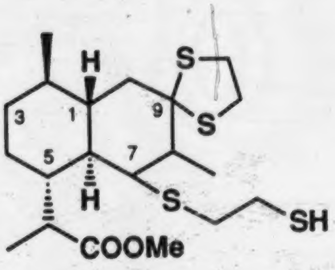
Jones reagent (0.5 ml) was added to a solution of **160** (204.7 mg, 0.875 mmol) in acetone (7 ml, distilled from potassium permanganate) at 0°C. After stirring for 3.5 h, water was added and the mixture was extracted with dichloromethane. The combined extracts were dried, filtered and concentrated to give the crude acid.

Anhydrous potassium carbonate (286.9 mg, 2.08 mmol) was added to a solution of the above acid in acetone (7 ml, distilled over potassium permanganate) at room temperature. The mixture was allowed to stir for 30 min and 0.54 ml (8.75 mmol, 10 eq) of methyl iodide was then added. After 17 h, the mixture was filtered, washed with dichloromethane and the filtrate was then concentrated. Flash chromatography with 10% ether in petroleum ether gave **161** (158.8 mg, 0.6 mmol) in 69% yield. The $^1$H NMR (300 MHz, $CDCl_3$) spectrum showed two sets of signals in an integral ratio of 1 : 3.6. The major compound showed signals at $\delta$ 6.74 (br s, 1H, $CH{=}CCH_3$), 3.72 (s, 3H, $OCH_3$), 1,79 (dd, 3H, $CH{=}CCH_3$, $J = 2.5$, 1.5 Hz), 1.08 (d, 3H, $H_3CCHCO_2CH_3$, $J$ = 7 Hz), 0.89 (d, 3H, $CHCH_3$, $J$ = 6.5 Hz). The minor compound showed signals at δ 6.85 (br s, 1H, $CH{=}CCH_3$), 3.70 (s, 3H, $OCH_3$), 1.79 (dd, 3H, $CH{=}CCH_3$, $J$ = 2.5, 1.5 Hz), 1.22 (d, 3H, $H_3CCHCO_2CH_3$, $J$ = 7 Hz), 0.89 (d, 3H, $CHCH_3$, $J$ = 6.5 Hz). The following spectral data was also obtained for the mixture: FT-IR 1727 (C=O, ester), 1663 (C=O, conjugated) $cm^{-1}$; HRMS $M^+$ 264.1724 (calcd. for $C_{16}H_{24}O_3$: 264.1725).

### (1S, 6R, 7R, 10R)-7-(1-Carbomethoxyethyl)-3,3-ethylenedithio-4,10-dimethylbicyclo[4.4.0]dec-4-ene (162) and (1S, 2R, 5R, 6R, 7S(R), 8S(R))-5-(1-carbomethoxyethyl)-9,9-ethylenedithio-2,8-dimethyl-7-(2-thiolethylenethio)bicyclo[4.4.0]decane (163)



162



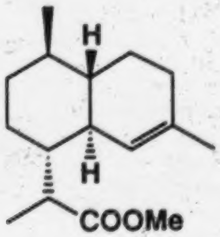
163

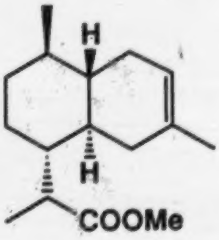
1,2-Ethanedithiol, 15 μl (0.179 mmol, 1 eq) and boron trifluoride etherate (10 μl, 0.08 mmol, 0.5 eq) were added to a solution of enone **161** (46.7 mg, 0.177 mmol, mixture of 1 : 4.7) in dichloromethane (1.5 ml, dried) at 0°C, under an atmosphere of argon. The reaction mixture was stirred for 43 h and 1 ml of 1 *M* aqueous sodium hydroxide solution was added. The organic layer was separated, washed with 1 *M* aqueous sodium hydroxide solution (3 x), dried, filtered and concentrated. Flash chromatography of the residue with 5-10% ether in petroleum ether gave **162** (18.1 mg, 0.053 mmol) in 30% yield. The $^1$H NMR (300 MHz, $CDCl_3$) spectrum showed two sets of signals in an integral ratio of 1 : 4.7. The major compound showed signals at $\delta$ 5.67 (br s, 1H, C**H**=$CCH_3$), 3.65 (s, 3H, OC**H**$_3$), 3.31 (m, 4H, SC**H**$_2$C**H**$_2$S), 2.91 (ddd, 1H, *J* = 14, 7, 3 Hz), 2.52 (dd, 1H, $S_2$CCH**H**, *J* = 13, 2 Hz), 1.97 (dd, 3H, CH=CC**H**$_3$, *J* = 2.5, 1.5 Hz), 1.15 (d, 3H, **H**$_3$CCHC$O_2$C$H_3$, *J* = 7 Hz), 0.94 (dd, 3H, CHC**H**$_3$, *J* = 6 Hz). The minor compound showed signals at $\delta$ 5.51 (br s, 1H, C**H**=$CCH_3$), 3.68 (s, 3H, OC**H**$_3$), 3.31 (m, 4H, SC**H**$_2$C**H**$_2$S), 2.95 (ddd, 1H, *J* = 14, 7, 4 Hz), 2.55 (dd, 1H, $S_2$CCH**H**, *J* = 13, 1.5 Hz), 1.97 (dd, 3H, CH=CC**H**$_3$, *J* = 2.5, 1.5 Hz), 1.01 (d, 3H, **H**$_3$CCHC$O_2$C$H_3$, *J* = 7 Hz), 0.94 (dd, 3H, CHC**H**$_3$, *J* = 6 Hz). The mixture also showed the following spectral data: FT-IR 1733 (C=O, ester) cm$^{-1}$; HRMS M$^+$ 340.1524 (calcd. for $C_{18}H_{28}O_2S_2$: 340.1531). Further elution gave compound **163** (27.5 mg, 0.063, 36% yield): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.69 (s, 3H, OC**H**$_3$), 0.84-3.36 (aliphatic H); FT-IR 1734 (C=O, ester) cm$^{-1}$; HRMS M$^+$ 434.1446 (calcd. for $C_{20}H_{34}O_2S_4$: 434.1442).

Compound **162** could also be prepared by the following procedure:
Enone **161** (10.1 mg, 0.038 mmol) in 0.5 ml benzene was added dropwise to a refluxing mixture of *p*-toluenesulfonic acid (17 mg, 0.088 mmol) and 1,2-ethanedithiol (3 µl, 1 eq) in 0.5 ml of benzene. The mixture was refluxed for 0.5 h and cooled to room temperature . Aqueous 1 *M* sodium hydroxide solution (2 ml) was then added and the mixture was extracted with

dichloromethane (2 x 3 ml). The combined dichloromethane extracts were washed with 1 *M* aqueous sodium hydroxide solution, dried, filtered and concentrated. Flash chromatography with 5% ether in petroleum ether gave compound **162** (8.4 mg, 0.025 mmol) in 65% yield.

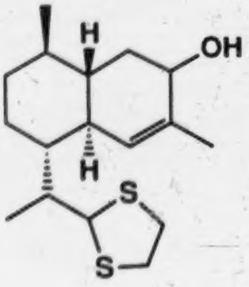
### (1S, 6R, 7R, 10R)-7-(1-Carbomethoxyethyl)-4,10-dimethylbicyclo[4.4.0]dec-3-ene and (1S, 6R, 7R, 10R)-7-(1-carbomethoxyethyl)-4,10-dimethylbicyclo[4.4.0]dec-4-ene (164)





To a solution of **162** (16 mg, 0.047 mmol, mixture of 1 : 4.7) in ethanol (0.5 ml) was added a suspension of Ra-Ni W2 (0.5 $cm^3$) in 3 ml of ethanol. The mixture was stirred at room temperature for 1.5 h and then filtered through a layer of silica gel in a sintered funnel. The solid residue was washed with ether and the filtrate was then concentrated. Flash chromatography with petroleum ether gave a 1 : 2 : 2 : 3 mixture of compound **164** (7 mg, 0.028 mmol) in 60% yield: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.51, 5.39 (vinylic), 3.66 ($OCH_3$), 1.66 ($CH{=}CCH_3$), 1.15 ($H_3CCHCO_2CH_3$), 0.89 ($CHCH_3$); FT-IR 1737 (C=O, ester) $cm^{-1}$; HRMS $M^+$ 250.1927 (calcd. for $C_{16}H_{26}O_2$: 250.1933).

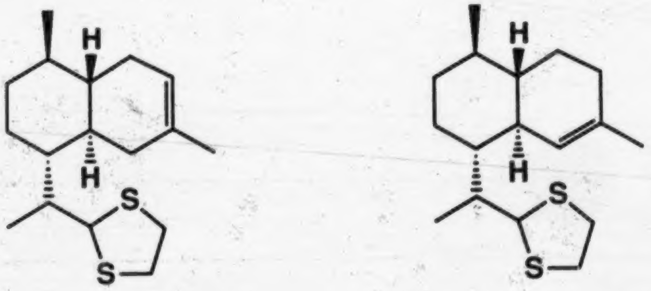
### (1S, 3S(R), 6R, 7R, 10R)-7-(1-Methyl-2,2-ethylenedithioethyl)-4,10-dimethylbicyclo[4.4.0]dec-4-en-3-ol (165)



To a solution of **159** (131.5 mg, 0.562 mmol) in dichloromethane (3 ml) at 0°C, was added 1,2-ethanedithiol (50 µl, 0.596 mmol, 1.06 eq) and boron trifluoride etherate (70 µl, 0.562 mmol). After 5 min, 10 ml of dichloromethane was added and the organic layer was washed with 1 *M* aqueous sodium hydroxide solution (3 x 2 ml). The organic layer was then dried, filtered and concentrated.

To a solution of the above crude thioacetal in 3 ml of methanol and 812.2 mg of $CeCl_3 \cdot 7H_2O$ at 0°C was slowly added 79.2 mg of sodium borohydride. After 1 h, the reaction was quenched with saturated ammonium chloride solution and extracted with dichloromethane. The organic extracts were dried, filtered and concentrated. Flash chromatography with 20% ether in petroleum ether gave compound **165** (99.3 mg, 0.318 mmol) in overall 57% yield. The $^1H$ NMR (300 MHz, $CDCl_3$) spectrum showed two sets of signals in an integral ratio of 1 : 2.5. The major compound showed signals at δ 5.55 (br s, 1H, **CH**=$CCH_3$), 4.44 (d, 1H, $S_2$**CH**, *J* = 10 Hz), 4.15 (m, 1H, **CH**OH), 3.22 (m, 4H, S**CH$_2$CH$_2$**S), 2.38 (ddd, 1H, HOCHC**H**H, *J* = 12, 6, 2 Hz), 2.20 (dddd, 1H, *J* = 13, 7, 7, 3 Hz), 1.77 (br s, 3H, CH=C$CH_3$), 0.98-1.77 (m, 10H), 0.98 (d, 3H, CH$CH_3$, *J* = 7 Hz), 0.90 (d, 3H, CH$CH_3$, *J* = 6 Hz). The minor compound showed signals at δ 5.60 (m, 1H, CH=C$CH_3$), 4.63 (d, 1H, $S_2$CH, *J* = 6 Hz). The mixture also showed the following spectral data: FT-IR 3380 (OH) $cm^{-1}$; HRMS $M^+$ 312.1573 (calcd. for $C_{17}H_{28}OS_2$: 312.1581).

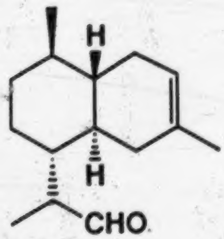
**(1S, 6R, 7R, 10R)-7-(1-Methyl-2,2-ethylenedithioethyl)-4,10-dimethylbicyclo[4.4.0]dec-3-ene and (1S, 6R, 7R, 10R)-7-(1-methyl-2,2-ethylenedithioethyl)-4,10-dimethylbicyclo[4.4.0]dec-4-ene (166)**

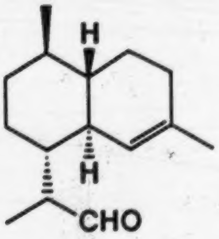


Methanesulfonyl chloride (40 µl, 0.515 mmol) and triethylamine (80 µl, 0.586 mmol) were added to a solution of **165** (36.6 mg, 0.117 mmol, in the ratio of 1 : 1.6) in 2 ml of dichloromethane at 0°C under an argon atmosphere. After 3.5 h, 2 ml of 1 *M* hydrochloric acid was added. The organic layer was separated and the aqueous layer was extracted with ether (2 x 3 ml). The combined organic extracts were dried, filtered and concentrated.

To a suspension of lithium aluminium hydride (41.6 mg, 1.09 mmol) in 1 ml of tetrahydrofuran (dried) was added a solution of the above mesylate in 2 ml tetrahydrofuran under an argon atmosphere. The mixture was refluxed for 1 h and cooled to room temperature. The excess hydride was destroyed by the addition of ethyl acetate and 1 *M* hydrochloric acid. Then the mixture was extracted with ether (3 x 4 ml) and the combined extracts were dried, filtered and concentrated. Flash chromatography with petroleum ether gave a mixture of **166** (26.4 mg, 0.089 mmol, 76% yield) as a colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 5.50, 5.45, 5.37 (m, C**H**=$CCH_3$, in the ratio of 12 : 13 : 7 respectively), 4.67, 4.45 ($S_2C$**H**), 3.21 (m, 4H, $SC$**H**$_2$C**H**$_2$S), 1.66 (CH=CC**H**$_3$); HRMS M$^+$ 296.1634 (calcd. for $C_{17}H_{28}S_2$: 296.1632).

### (1S, 6R, 7R, 10R)-7-(1-Formylethyl)-4,10-dimethylbicyclo[4.4.0]-dec-3-ene and (1S, 6R, 7R, 10R)-7-(1-formylethyl)-4,10-dimethylbicyclo[4.4.0]dec-4-ene (167)





To a solution of thioacetal **166** (26.2 mg, 0.088 mmol) in 2 ml of 80% aqueous acetonitrile was added mercury(II) chloride solution (131.9 mg, 0.486 mmol in 1 ml 80% aqueous acetonitrile). After stirring at room temperature for 24 h, the mixture was filtered through a layer of silica gel in a sintered funnel. The filtrate was concentrated and the residue was dissolved in dichloromethane. The dichloromethane layer was washed with water (3 x), dried, filtered and concentrated. Flash chromatography on silica gel using petroleum ether as eluant recovered **166** (4.4 mg, 0.015 mmol). Further elution with 4% ether in petroleum ether gave a mixture of **167** (3.9 mg, 0.018 mmol, 24% yield): $^1$H NMR (300 MHz, $CDCl_3$) δ 9.83, 9.82, 9.80, 9.67 (CHO, integral ratio of 2 : 7 : 3 : 7 respectively), 5.39, 5.26 (vinylic), 0.80-2.10 (aliptic H); FT-IR 1722 (C=O) cm$^{-1}$; HRMS M$^+$ 220.1826 (calcd. for $C_{15}H_{24}O$: 220.1827).

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